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Original Communications

HEART PUNCTURE IN MAN FOR DIODRAST VISUALIZATION OF THE VENTRICULAR CHAMBERS AND GREAT ARTERIES

I. ITS EXPERIMENTAL AND ANATOMOPHYSIOLOGICAL BASES AND TECHNIQUE

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IT IS known that cardiac physiology has been enriched by thoracic surgery, especially through surgical interventions on cardiac valves, either experimentally or on human subjects,[1] as well as by surgery of the aorta[2] and the pulmonary artery.[3] It is also known that great contributions have been obtained by the valuable data gained through cardiac catheterization, either of the right-[4] or left-sided[5] cavities and aorta.

Yet, on the other hand, in order to obtain direct information concerning the activities of the heart, it is necessary to gain it on the operating table, taking advantage of an intervention on the heart proper or the neighboring organs, or to accept the data of cardiac catheterization, risking any error which might arise from this, especially in regard to physiological preciseness.

These facts led us to consider the possibility of a method which might facilitate the direct approach to the cardiac ventricles, eliminating the application of certain instruments or utensils whose mechanism might alter the final results of the investigation or even harm the vessels or the endocardium.[6]

We believe that besides the physiological aspects of the question and the pathological alteration, such as the direct intraventricular pressure, gasometry of the blood of the cavities, and the introduction of some therapeutic agents, this direct and simple procedure would enable us to visualize the ventricles, the aorta, and the pulmonary artery and its branches with exactitude.

We have also considered the possibility of direct intraventricular transfusion in shock or in massive hemorrhage, as it has been known that "when large amounts of blood are transfused into a vein of a patient with a severely

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depleted blood volume and lowered blood pressure, a sudden burden is placed upon the right heart and then upon the left heart before any improvement occurs in the coronary blood flow."[7]

We considered, therefore, that the possibility of such a method should be explained, as it might reveal new, and perhaps unexpected, results. It thus occurred to us to try the direct cardiac puncture by means of a trocar, with its mandrel, as an exploratory method.

We did not underestimate the fact (before and after experiments on dogs and the harmless use of the procedure on forty-five patients) that this idea would provoke aversion, arouse criticism, and be considered an inhumane method. This reaction would be quite natural for two reasons: first, because of the unique fact that the heart was the organ to be punctured, and, second, because of the blindness of the method, that is, operating without having at sight the coronary vessels. This would not be dangerous if we could prove on the animal or on the cadaver the area to be punctured in relation to the distribution of the vessels.

We were concerned, however, that the puncture might produce bleeding when the trocar was withdrawn. It was after reading a paper by Ravitch and Blalock[8] that we started using the puncture method. These authors reported eight cases of cardiac tamponade caused by heart wounds, seven of which were treated only by pericardial aspiration, and all patients survived without complications. They added: "It is interesting that from these 8 cases, on which the tamponade was successfully treated by applying aspiration alone, 3 were of bullet wounds, 2 of knife wounds, and 2 only of icepick wounds."

In 1933, Reboul and Racine,[9] having applied direct heart puncture, published an experimental study on dogs concerning radiology of the ventricles; they did not propose its application to man in their conclusions. With the exception of punctures carried out with needles in cases of utmost emergency and for therapeutic reasons, this is the first time, so far as we know, that a systematic study of heart puncture in man has been made. The work of Hesse and Minkus,[10] who experimented on themselves to study ventricular movements with needles introduced into the heart through the third and fourth intercostal spaces, appears rather as an attempt at scientific exhibitionism than as a serious contribution to the kymographic study of the heart.

EXPERIMENTAL DATA

The experimental study on dogs was divided into two parts: (1) observation of the effects of the trocar without operating on the animal and (2) puncture and operation in order to make direct observations.

Effects of Trocar Without Operating.—The puncture, carried out on the first animals by a subxiphoid approach and with the same trocar used on man, produced a tachycardia which was maintained while the trocar was in place. As the trocar was introduced toward the myocardium, a slight touch on the ventricular wall produced noncontinuous extrasystoles. The pressure of the trocar on the ventricular wall, even though the trocar did not penetrate into the cavities, showed a simple lesion pattern on the electrocardiogram which disappeared the moment this pressure ceased.

Puncture and Operation.—With the trocar introduced and following the axis of the body, we made a thoracotomy through the fourth left intercostal space with resection of the anterior two-thirds of the fourth, fifth, and sixth ribs up to their sternal portions.

With insignificant variations, almost every time the end of the trocar reached the portion of the right ventricle that is in direct relation to the diaphragm. Never did the trocar touch the coronary vessels.

Regardless of the local use of a 1½ per cent solution of procaine, while the trocar was introduced into the heart wall, it produced extrasystoles. Although these extrasystoles would appear occasionally after the trocar had been introduced into the ventricular cavities, this happened very seldom.

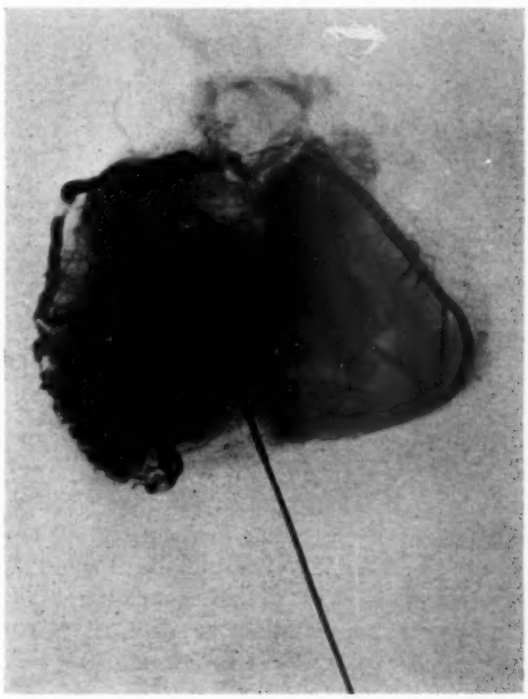

Fig. 1.

When the trocar was left to follow freely the movements of the heart, alterations of the rhythm could be observed, but these disappeared when the trocar was put under control.

The injection of 20 c.c. of 0.75 per cent of sodium chloride solution under pressure of 20 pounds, either into the right or into the left ventricles of an animal weighing 42 pounds, produced no objective alteration in the size of these cavities.

When the trocar was withdrawn, a drop of blood came out at the spot on which the puncture had been made, but no further bleeding was observed.

The autopsy of these animals showed no alterations of the heart worthy of note.

ANATOMICAL DATA

From the anatomical point of view, we have to call attention to certain data in regard to the place of the puncture.

The puncture is made on the inferior face of the right ventricle which abuts upon the diaphragm where no important coronary vessels can be found, as may be seen in Fig. 1 showing a heart injected with the dye with a trocar in the usual position as applied in our method.

If it turns out to be necessary to cross the interventricular septum, on its lowest portion.

This has been verified on cadavers of dogs with the trocar left in position when the sternum and rib cartilages were opened later.

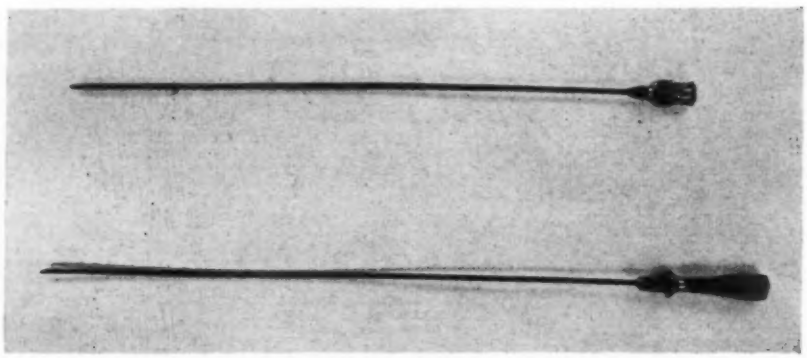

Fig. 2.

PHYSIOLOGICAL DATA

From the physiological point of view, the heart is to be considered a muscle, acting as such, although its fibers have special characteristics.

As regards its excitability, it should be remembered that the heart is not always equally excitable; this depends on its state of activity. During systole the heart is refractory to whatever kind of stimulation, no matter how strong it may be. This represents the period of systolic or periodic inexcitability, which is of importance in the appearance or nonappearance of extrasystoles. It depends on the moment at which the puncture is made.

Finally, it must be emphasized that the cardiac muscle responds to the law of "all or nothing," which means that once it is excited by an efficient stimulus, it contracts up to the maximum or not at all.

TECHNIQUE

Instruments.—We use a trocar 5½ inches long from the tip to the end to which a syringe may be connected. The exterior diameter of this trocar is 1.7 mm., and the lumen is 1.2 mm. It has a mandrel which does not overreach the end of the trocar (Fig. 2). This end is neither too sharp nor too dull.

To inject the dye we use the Dos Santos injecting apparatus, modified by Milanes and Perez Stable.[11]

Technique of Puncture.—To make the puncture we use gaped sterile towels and gloves; the skin is prepared with Merthiolate. Before starting with the puncture, the patient is given atropine sulfate (¼ mg.) in order to avoid the laryngeal spasm which could be produced by Pentothal. We use the latter as an anesthetic intravenously by injecting only 0.25 Gm., which is sufficient since the intervention takes a short time only. A few hours before starting with the puncture, we make an iodine test, introducing a drop of the substance to be used (70 per cent Diodrast solution) into the conjunctival sac to avoid accidents of iodism.

The patient is placed in the supine position to enable us to reach any of the ventricles. When a view of the aortic arch and of the descendent aorta is desired, the puncture is performed with the patient in a lateral position. Once the patient is in the proper position, the electrodes are fixed to take electrocardiographic tracings before, during, and after the puncture.

Fig. 3.

After the patient is anesthetized, we seek with the index finger of the left hand the space between the xiphoid process at the left and the seventh costal cartilage of the same side. We thus touch the heart by an epigastric paraxiphoid puncture, resembling the procedure of tapping the pericardium applied by Marfan[12] (Fig. 3).

Two sensations are felt during the introduction of the trocar. One is when the first resistance to the trocar is noticed as it enters the pericardium; the other is the sensation of cardiac contraction itself reflected at the end of the trocar.

The penetration into the ventricular cavities can be proved by the rhythmical movements of the trocar and, when the mandrel is withdrawn, by the presence of dark blood from the right ventricle and of scarlet blood from the left ventricle. The dribbling way the blood comes out of the right ventricle and the pulsating way it comes from the left are also characteristic.

Once the trocar has been introduced into the cavities, it is possible to register the intraventricular pressure. On one occasion (Figs. 4 and 5) this was done with an electromanometer (Sanborn).*

An x-ray picture of the ventricular cavities, of the aorta, and of the pulmonary artery, as well as of the coronary arteries, can be obtained by injecting 50 to 80 c.c. of Diodrast under a pressure of 25 pounds into the right ventricle and of 35 pounds into the left one. We call this method "cardioangiography," since the films are taken from the heart toward the vessels (Fig. 6).

Fig. 4.

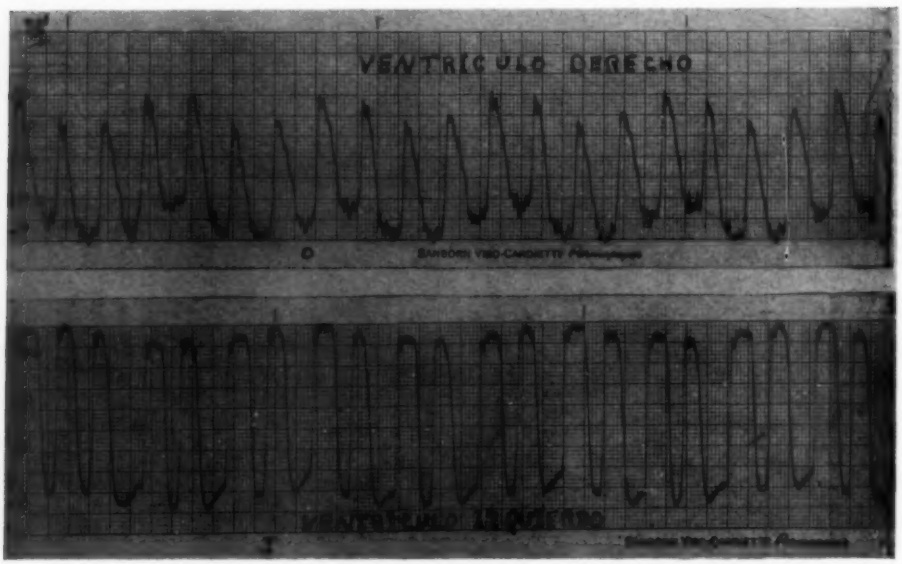

Fig. 5.

In one of our cases the trocar was introduced too deeply, and we obtained a real pericardiography (Fig. 7).

Once the puncture has been made, the trocar is withdrawn without bleeding. The patient returns to his bed fully awake, and he is checked radiologically and electrocardiographically up to ten days after the puncture.

CONCLUSIONS

1. The experimental and anatomophysiological bases, as well as the technique, of heart puncture on man have been studied.

2. This technique has been applied forty-five times on thirty patients without mortality or any untoward results.

3. This is the first time, so far as we know, that cardiac puncture has been applied systematically with a trocar in man.

*By Professor Stanley J. Sarnoff from the Department of Public Health of the Harvard Medical School, who was kind enough personally to take the tracings. We are deeply obligated to him and to his assistant Dr. J. V. Maloney from Johns Hopkins.

Fig. 6.

Fig. . 7

We are indebted to Professor Durán Quevedo, from the Physiology Department of our University, for his aid in the experimental part of this work. Much help in a direct way has been given by Dr. Luis Ricardo, Dr. Sentí Paredes, and Dr. Carlos Bujosa. To all of these go our acknowledgment and thanks.

ADDENDUM

This paper was read before the Society for Clinical Studies of Havana, Cuba, May 18, 1950. After this, and until June 20, 1950, fifty-six punctures were made without mortality.

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ELECTROCARDIOGRAPHIC CHANGES DURING ANGIOCARDIOGRAPHY

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ANGIOCARDIOGRAPHY is a diagnostic procedure which consists of the rapid intravenous injection of a contrast substance followed by roentgenographic examination of the chest at multiple or appropriate intervals. In this manner, contrast visualization of the chambers of the heart and the great blood vessels may be obtained. Since its introduction by Robb and Steinberg in 1938,[1] the method has proved to be productive in the diagnosis of a variety of congenital and acquired diseases of the heart and chest.[2] Although death has not followed in over 1,650 angiocardiographic injections at The New York Hospital, the procedure is not without hazard, as has been shown by a recent summary of twenty-six deaths following angiocardiography.[3] Death, which in thirteen cases occurred within an hour of the time of injection, was often ascribed to respiratory arrest. Detailed physiological observations of the mechanism of death were not made and autopsy studies were, in general, unrewarding. A study of certain physiologic responses to angiocardiography with Diodrast in the anesthetized dog has recently been reported by Gordon and associates.[4] In an attempt to explore a possible mechanism of death following angiocardiography, the following electrocardiographic investigation was undertaken. Howarth[5] studied the blood pressure changes during the angiocardiographic injection of diodone and noted the presence of "irregularities" in the electrocardiograms of two cases.

METHOD

Sixteen patients undergoing angiocardiography for a variety of diagnostic purposes constituted the case material. A total of twenty-one injections was made, the patients reclining during the duration of study. After a ten-minute rest period a control electrocardiographic tracing was made, following which, during the continuous recording of Lead II or the standard limb leads and CF_4, a rapid injection (duration 1 to 3 seconds) of Diodrast (70 per cent) or Neoiopax (75 per cent) was given. Dosage of contrast substance was of the amount usually used for angiocardiography. Following the injection, continuous tracings of Lead II or the four leads were recorded for at least five minutes, short records being made at one-minute intervals thereafter for a total of ten minutes.

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In most cases, the three standard limb leads were recorded at the end of each minute. A Sanborn direct-writing Poly-Viso recording galvanometer was used. Wherever repeated injections were made on the same patient, a period of at least fifteen minutes was allowed between injections. Save for one instance (a 5-year-old child studied under ether anesthesia), the patients were unanesthetized and had no preliminary medication.

RESULTS

Change in Heart Rate.—In the twenty-one injections of contrast media in sixteen patients there was an increase in cardiac rate in twenty of these and a decrease in one. The maximum rate following the injection was determined in each instance. The increases in rate varied from four per minute to as high as sixty-nine per minute. The average increase in heart rate was 27.3 beats per minute for the twenty instances showing elevations of rate.

Changes in Form of the Electrocardiogram.—The changes in T waves and RT segments following the injections were striking. These varied from a slight decrease in amplitude of the T wave to flattening and inversion of the waves with coving. The first changes in the T waves, a slight decrease in amplitude, were noted at approximately 10 seconds and the maximum changes at an average time of 16 seconds. RT segment depression occurred in ten of the subjects along with the T-wave changes. There were five instances in which the T waves became negative and coved, two following Diodrast and three following Neo-iopax. In the majority of cases the changes in the T waves, as well as the RT segment changes, had returned to their preinjection form in 60 seconds, although in some cases it took several minutes. The time of onset of the changes was that which would be required for the drug to reach the systemic arteries including the coronary vessels, namely 7 to 10 seconds.

Typical examples of changes seen in the electrocardiogram following the rapid intravenous injection of contrast substance are depicted in Fig. 1,*A*. In this case 50 c.c. of 70 per cent Diodrast were rapidly injected intravenously in a 65-year-old man. The resting or control electrocardiogram was normal, and thereafter Lead II was taken continuously during and following the injection. The only changes that occurred were an increase in heart rate and a slight decrease in amplitude of the T wave. In contrast to this were the changes in the electrocardiogram following the rapid intravenous injection of 50 c.c. of 75 per cent Neo-iopax in the same patient (Fig. 1,*B*). The T wave became negative and coved. The first T-wave changes in both instances were noted at 11 seconds and 9 seconds, respectively, with the maximum changes at 15 and 12 seconds.

Changes in Rhythm.—No abnormal rhythms developed. However, following nine of the injections auricular or ventricular premature contractions or both occurred. There were two subjects who had both auricular and ventricular premature contractions. One of these showed marked slowing of the heart rate and two ventricular premature contractions in sequence (Fig. 2,*A*). Multiple auricular premature contractions occurred in two subjects (Fig. 2,*B*). One of these subjects also had an occasional aberrant spread of the excitation wave

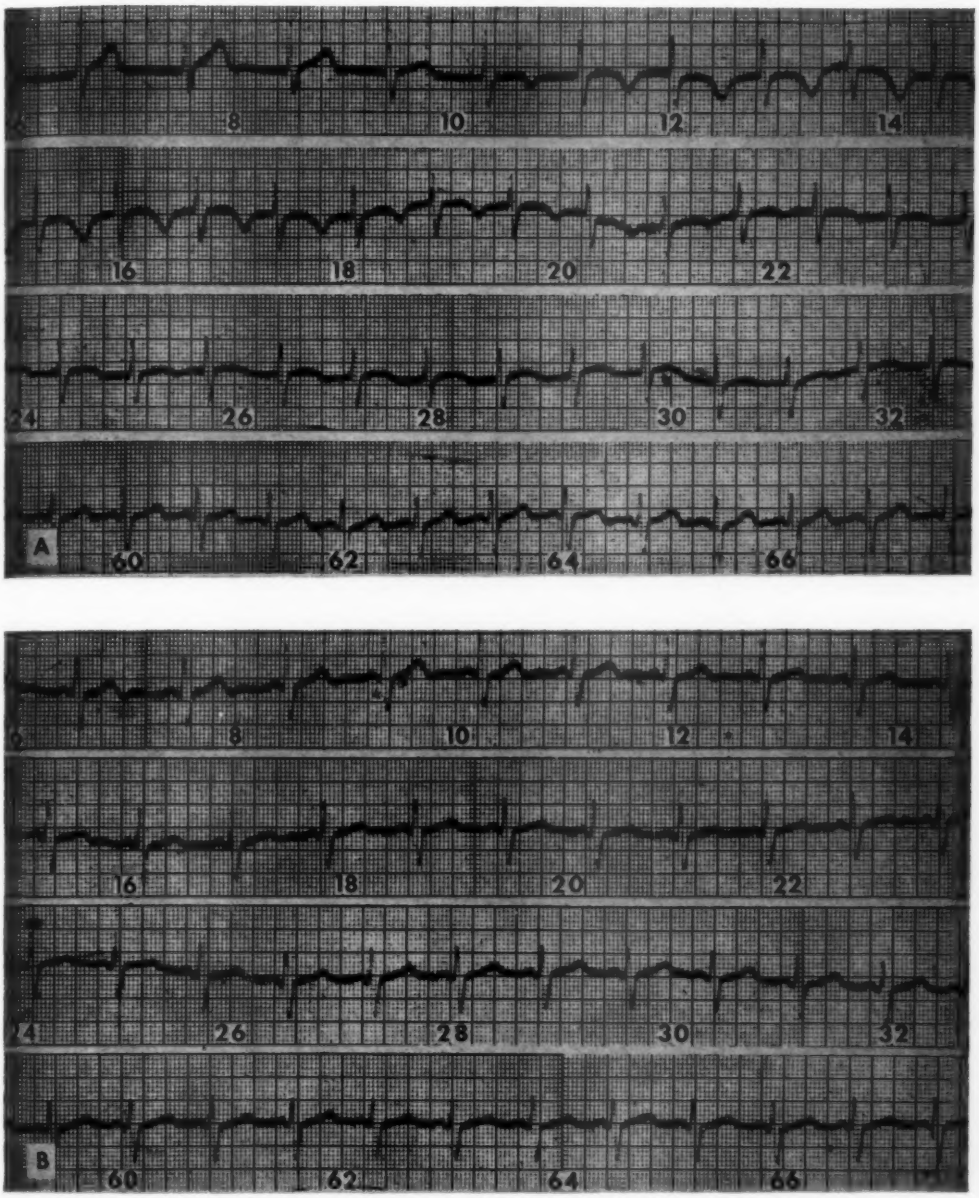

Fig. 1.—*A*, Electrocardiogram following the rapid intravenous injection of 50 c.c. of 70 per cent Diodrast in a 65-year-old man. The control limb leads were normal. Lead II was taken continuously following the injection. There is a slight increase in the heart rate and a slight decrease in the amplitude of T_2, the first change occurring 11 seconds following the injection with the maximum decrease in amplitude at 15 seconds. Between 60 and 80 seconds the amplitude of the T wave returned to its control form. *B*, Electrocardiogram following rapid intravenous injection of 50 c.c. of 75 per cent Neo-iopax in the same patient as shown in *A*. Lead II was taken continuously. Marked T-wave changes occurred. At 9 seconds the T wave began to decrease in amplitude, and at 12 seconds it had become negative and coved. Between 60 and 80 seconds the T wave returned to its control form.

(Fig. 2,*C*). Two of the remaining subjects had only auricular premature contractions, and three had only occasional ventricular ectopic beats.

DISCUSSION

The significance of these changes following rapid angiocardiographic injections can only be speculated upon. In view of the fact that the contrast substance reaches the coronary arteries on the average of 7 to 10 seconds after the injection, the average time of onset and maximal T-wave changes (10 and 16 seconds, respectively) point to a myocardial change. This might be the result of coronary spasm, hemodilution, a direct effect upon the myocardium, or externally mediated reflex activity. The electrocardiographic changes observed in this study, namely tachycardia, flattening and inversion of the T waves, and

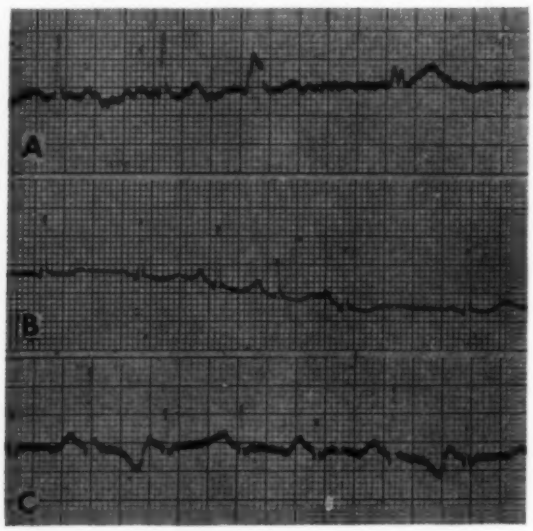

Fig. 2.—*A*, Bradycardia and ventricular premature contractions in sequence 10 seconds following the injection of 50 c.c. of 75 per cent Neo-iopax in a 53-year-old woman. *B*, Multiple auricular premature contractions 18 seconds following the injection of 45 c.c. of 70 per cent Diodrast in a 41-year-old woman. *C*, Aberrant spread of the excitation wave 50 seconds following the injection of 50 c.c. of 75 per cent Neo-iopax in a 23-year-old man.

depression of the RT segments, are similar to those seen in the electrocardiogram in acute coronary insufficiency and with positive anoxemia and exercise tolerance tests. Since the positivity of these tests is thought to be dependent upon an insufficient coronary circulation and since the observed changes in this study resemble those seen in such tests, it seems reasonable to assume that the contrast substance produces some change in the coronary circulation with resulting myocardial anoxia.

In the patient shown in Fig. 1, the changes following Neo-iopax were more marked than those following Diodrast. However, marked changes in T waves were observed following Diodrast injections in other patients, suggesting that individual drug sensitivity may play a role in the reaction.

It is possible that in subjects with coronary artery disease, the rapid intravenous injection of contrast agents might produce myocardial anoxia of sufficient magnitude to result in myocardial infarction and death. In subjects with inadequate coronary circulation such as may be caused by congenital or pulmonary heart disease, it is possible that added anoxia as a result of the injection might be catastrophic. Although there is thus far no pathological evidence that this has occurred, sudden death due to myocardial anoxia may escape post-mortem recognition. Anginal pain is rarely encountered following angiocardiography.

A further possible factor in death following angiocardiography is the onset of an abnormal rhythm. Nine of the subjects in this series developed auricular or ventricular premature contractions, suggesting the potentiality of ventricular paroxysmal tachycardia as a complication of angiocardiography.

The results of this study fail to confirm preliminary observations[6] that electrocardiographic changes of importance do not accompany angiocardiographic injections.

CONCLUSIONS

1. Continuous electrocardiographic tracings indicate that concomitant with the arrival of the contrast substance in the coronary arteries during angiocardiography there occur changes compatible with or suggestive of temporary myocardial anoxia.

2. Myocardial anoxia may conceivably participate in death following angiocardiography, particularly when an already overtaxed myocardium is involved.

ADDENDUM

Personal communication with Dr. Gerrold Lieberman, Second Medical Division, Bellevue Hospital, disclosed that left bundle branch block, bradycardia (heart rate 48 to 56), and fall in blood pressure from 240/120 to 160/90 mm. Hg followed the angiocardiographic use of Diodrast in a 49-year-old man. Spontaneous recovery took place within two hours.

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BUNDLE BRANCH BLOCK WITHOUT SIGNIFICANT HEART DISEASE

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AS A result of a study of 5,000 electrocardiograms, a point of view has been reached which is at variance with that usually held concerning bundle branch block. Briefly, the conclusion is that in a considerable percentage of cases this electrocardiographic pattern is not an expression of any clinically definable morbid anatomy or physiology. This applies chiefly in regard to right bundle branch block. While this opinion is not an original one, it is worthy of reiteration in view of the increasingly widespread use of the electrocardiograph as a diagnostic aid, and the consequent danger of establishing cardiac invalidism in otherwise essentially healthy persons with bundle branch block because of improper clinical interpretation.

It is recognized that the usual analysis of the occurrence of bundle branch block is correct if the material is obtained from hospital or ordinary outpatient department practice. However, as will be mentioned, because of the material utilized, this study probably gives a more comprehensive view of the significance of the electrocardiographic pattern in question.

MATERIAL

The cases studied were encountered in the routine work of the Cardiac Clinic, Veterans Administration Regional Office, Dallas, Texas. Two groups of veterans are examined at this clinic—individuals with service-connected cardiovascular disorders seen for treatment purposes and individuals undergoing examination in connection with pension problems. Members of the latter group are referred to the clinic for a variety of reasons which include: (1) correct previous diagnosis of cardiovascular disease, (2) incorrect previous diagnosis of cardiovascular disease, (3) suspicion on the part of the general medical examiners that cardiovascular disease might be present, (4) the feeling on the part of some of the examinees that their subjective sensations might represent cardiovascular disease, and (5) clerical errors. The composition of the clientele of the clinic thus approximates that of an office practice in cardiology, rather than that of a charity cardiac clinic from which persons in the latter 2 categories would have been eliminated by examination in the general medical clinics. The material was not unduly weighted by the use of previously diagnosed cases, as two-thirds of the bundle branch block group were found to have this abnormality for the first time at the current examination.

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A careful history, a physical examination of the fundi, peripheral vessels, thoracic and abdominal organs, electrocardiogram, and x-ray examination of the chest were obtained in each case. Fluoroscopic examination of the heart, circulation time tests, vital capacity measurements, and appropriate laboratory examinations were done when indicated.

Fifty-two of the veterans who had the 5,000 electrocardiograms were found to have patterns characteristic of bundle branch block. Almost all of the tracings included multiple chest leads and the augmented unipolar limb leads; the few which were not complete showed definitely diagnostic conventional limb leads. None of the 52 tracings was of the Wolff-Parkinson-White type of aberrant conduction. The criteria for classification of the cardiograms were those of Wilson and his co-workers.[1]

RESULTS

Tables I and II include a brief summary of each case with the electrocardiographic and the clinical diagnoses. Seventeen patients showed left bundle branch block, and 35 showed right bundle branch block. A diagnosis of organic cardiac disease was made in the presence of any of the following: (1) an adequate history of the anginal syndrome, (2) a history of myocardial infarction, (3) a history of significant dyspnea in the absence of pulmonary disease, if supported by any physical signs suggestive of cardiac disease, (4) enlargement of the heart or signs indicative of (5) valvular or (6) congenital cardiac disease.

With the use of these criteria, 19 individuals were found to have organic cardiac disease. There were, in addition, 9 with hypertensive disease who had no complaints referable to the heart and no enlargement of the heart. These were not considered to have organic cardiac disease. Thirty-three patients had no evidence of cardiac disease.

Right bundle branch block occurred 35 times, and left bundle branch block occurred 17 times. Of the group of 35, 9 had organic cardiac disease, and 26, or 74 per cent, had no evidence of organic cardiac disease. Of the 17 patients with left bundle branch block, 10 did and 7, or 41 per cent, did not show evidence of organic cardiac disease. Thus, 63 per cent of all the patients had no obvious cause for the presence of the abnormal pattern. This is the highest incidence of such patients in any sizable group reported to date.

Analysis of the cases according to age did not reveal anything of note, except that 27 per cent of the entire group were diagnosed before the age of 40 years (see Table III). Langley and associates[2] found a similar age incidence in their study originating in a naval hospital which probably had a larger number of young patients. Most of the patients with bundle branch block were first diagnosed between the ages of 50 and 60 years, but it should be remembered that most of the patients seen in the clinic fall into this age group.

The associated noncardiac diseases were those that might be expected in a predominantly older age group. Hypertension without cardiac disease was found 9 times, emphysema without involvement of the right side of the heart twice, and latent syphilis, chronic bronchitis, peptic ulcer, bronchiectasis, and

TABLE I.

CASE NO.	BRIEF CASE SUMMARY	DIAGNOSIS	AGE AT EXAMINATION	FIRST DIAGNOSED AS BBB AT AGE
	Left BBB With Heart Disease			
7	BBB found in 1940, routine examination; 1943, angina, LAD, inverted T_1, no BBB; 1944, dyspnea and angina, BBB present since; failure since 1941, mitral diastolic murmur at present	ASHD, RHD	44	34
8	1944, acute cardiac infarction; angina since; no EH or failure; Grade 3 aortic systolic; BP 190/110 mm. Hg	ASHD, HVD	64	60
11	Mild failure 6 months, on digitalis; has EH; BP 150/115 mm. Hg; Grade 2 systolic at apex and base	HCVD	58	58
25	1947, congestive failure, present intermittently since; EH; BP 170/110 mm. Hg	HCVD	62	60
27	1945, acute cardiac infarction, no cardiac complaints since; no EH; BP 130/80 mm. Hg	ASHD	28	23
31	Hypertension for 20 years; mild congestive failure 1 year; BP 160/110 mm. Hg; EH	HCVD	49	48
35	1940, bronchiectasis and BBB; 1942, EH; 1947, congestive failure, fairly well compensated since; EH, gallop, BP 120/70 mm. Hg; no murmurs; cylindrical bronchiectasis left base	Unknown etiology	46	39
42	EH, early congestive failure	HCVD	56	56
43	EH, angina, congestive failure	ASHD, HVD	58	58
44	1941, angina; 1942, BBB, no EH; BP 120/80 mm. Hg	ASHD	45	37
	Right BBB With Heart Disease			
4	1947, probable acute cardiac infarct; no EH; BP 220/140 mm. Hg; no angina	ASHD	57	56
16	1921, exertional dyspnea; 1949, auricular fibrillation apical Grade 3 systolic, BP 130/80 mm. Hg; borderline heart size; rheumatoid changes in fingers	RHD	52	52
17	Patent interventricular septum; no EH or symptoms; BP 130/80 mm. Hg	CHD	59	59
20	1945, murmur, no ARF; Grade 4 aortic systolic and soft early aortic diastolic; A_2 not heard; no EH; BP 120/80 mm. Hg; asymptomatic	RHD	35	35
22	Multiple cardiac infarcts, first in 1946; marked EH; gallop; frequent anginas; no congestive failure	ASHD	48	45
26	Congestive failure; BP 100/80 mm. Hg; EH; Grade 5 aortic systolic; A_2 absent	RHD	53	53

TABLE I.—CONT'D

CASE NO.	BRIEF CASE SUMMARY	DIAGNOSIS	AGE AT EXAMINATION	FIRST DIAGNOSED AS BBB AT AGE
	Right BBB With Heart Disease—Cont'd			
29	Angina for 1 year; BP 140/80 mm. Hg; no EH; Grade 3 aortic systolic; A_2 normal	ASHD	71	71
38	1944, angina; 1945, BBB; EH; no congestive failure; BP 210/130 mm. Hg	ASHD, HCVD	54	51
45	1947, angina; no EH; BP 160/110 mm. Hg	ASHD, HVD	59	59

BBB = Bundle branch block
LAD = Left axis deviation
EH = Enlargement of the heart
ASHD = Arteriosclerotic heart disease
HVD = Hypertensive vascular disease
HCVD = Hypertensive cardiovascular disease
ARF = Acute rheumatic fever
RHD = Rheumatic heart disease
CHD = Congential heart disease

TABLE II.

CASE NO.	BRIEF CASE SUMMARY	ASSOCIATED DISEASE	AGE AT EXAMINATION	FIRST DIAGNOSED AT AGE
	Left BBB Without Heart Disease			
14	No cardiac symptoms, no EH, normal exercise tolerance; BP 170/110 mm. Hg	HVD	57	57
18	BBB first known in 1938; alleged dyspnea and orthopnea for 15 years; noncardiac chest pain; tachycardia of gradual onset; BP 150/90 mm. Hg; no EH; Decholin time 14 seconds	Iatrogenic	58	47
28	Hyperventilation syndrome; hypertension known 15 years; no EH; BP 120/80 mm. Hg; Grade 1 apical systolic; auricular premature beats	None	55	55
36	Dyspnea and noncardiac chest pain since 1939; no EH; BP 120/80 mm. Hg; Grade 1 apical systolic murmur; auricular premature beats; chest roentgenogram negative	None	55	55
40	Noncardiac chest pain, relieved by exertion; BP 130/80 mm. Hg; no EH	Duodenal ulcer	32	31
47	Noncardiac chest pain; no EH; BP 160/90 mm. Hg; asthmatic attacks for 10 years; Decholin time 14 seconds; P-R interval 0.30; QRS 0.12	Probable asthma	55	55
50	Always tired; occasional palpitation; BP 135/90 mm. Hg; no EH; Decholin time 15 seconds	None	55	55

TABLE II.—CONT'D

CASE NO.	BRIEF CASE SUMMARY	ASSOCIATED DISEASE	AGE AT EXAMINATION	FIRST DIAGNOSED AT AGE
	Right BBB Without Heart Disease			
1	Noncardiac chest pain; no EH; BP 130/80 mm. Hg	Anxiety state	30	30
2	Noncardiac chest pain relieved by exertion; no EH; BP 130/90 mm. Hg	Anxiety state	56	55
3	No cardiac symptoms, EH, or murmurs; ARF in 1939; BBB diagnosed in 1943	Anxiety state	32	27
5	BBB diagnosed in 1945, anxiety state in regard to this; BP 130/90 mm. Hg; no EH	Iatrogenic	25	22
6	Hyperventilation syndrome and palpitation in 1945; BBB diagnosed in 1946 in Army, anxiety state in regard to this; 2:1 A-V block with RBBB in 1946; no A-V block since	Iatrogenic	27	23
9	No cardiac symptoms, no EH; Grade 1 systolic at apex and base; BP 150/90 mm. Hg	None	59	59
10	Noncardiac chest pain; dyspnea on climbing 1 flight; no EH; BP 140/90 mm. Hg	Arrested minimal tuberculosis	35	35
12	Noncardiac chest pain, relieved by exertion; no EH; combat reaction	Anxiety state	43	43
13	Dyspnea all the time, relieved by exertion; no EH; expiratory wheeze; BP 175/100 mm. Hg	HVD, emphysema	51	51
15	No cardiac symptoms; hypertension known 10 years; BP 165/95 mm. Hg; no EH	HVD	57	57
19	Noncardiac chest pain, chronic productive cough; chest roentgenogram negative; BP 130/80 mm. Hg; no EH	Chronic bronchitis	60	60
21	No cardiac symptoms; BP 200/100 mm. Hg; no EH; urine, 2 plus albumin, many RBC, occasional casts; latent syphilis	HVD, syphilis,? of nephritis	59	59
23	Hypertension known 3 years; BP 205/120 mm. Hg; no EH; no cardiac complaints; Decholin time 16 seconds; chest x-ray film shows emphysema, but there are no clinical signs of this	HVD, emphysema	56	56
24	Noncardiac pleuritic chest pain; BP 135/85 mm. Hg; no EH	Duodenal ulcer	43	43
30	Anxiety reaction in combat zone in 1943, BBB then; no change since; no EH; BP 125/85 mm. Hg	Anxiety state	40	34
32	No cardiac symptoms; BP 180/110 mm. Hg; no EH	HVD	58	58

TABLE II.—CONT'D

CASE NO.	BRIEF CASE SUMMARY	ASSOCIATED DISEASE	AGE AT EXAMINATION	FIRST DIGANOSED AT AGE
	Right BBB Without Heart Disease—Cont'd			
33	Since 1932 weakness and dyspnea on walking 100 feet; BP 110/80 mm. Hg; no EH; soft blowing systolic at apex and base; chest x-ray film negative	Anxiety state	55	55
34	No cardiac symptoms; BP 100/60 mm. Hg; referred through clerical error	None	29	29
37	Exertional dyspnea and noncardiac chest pain since 1945; after discovery of BBB during hospitalization for vague complaints, anxiety reaction increased by hospitalization; no EH; BP 120/70 mm. Hg	Iatrogenic	32	30
39	Hypertension known 5 years; dizziness, headaches, no cardiac complaints; BP 220/120 mm. Hg; no EH	HVD	53	53
41	No cardiac symptoms; chronic alcoholism; BBB discovered in Army work-up for alcoholism; diagnosed "myocarditis"; BP 140/80 mm. Hg; no EH	None	46	41
46	No cardiac complaints; BP 140/90 mm. Hg; no EH; ECG (twice) showed normal mechanism alternating with BBB singly and in runs without change in rate or rhythm; no WPW syndrome	None	55	55
48	Mild asthma in damp weather since 1919; no cardiac pain; hypertension known 3 years; BP 170/110 mm. Hg; no EH; chest x-ray film negative	HVD, asthma	57	57
49	Noncardiac chest pain 12 years; BP 150/90 mm. Hg; no EH	None	52	52
51	Hyperventilation syndrome; alleged pitting edema and paroxysmal dyspnea; BP 120/80 mm. Hg; no EH; chest x-ray film negative	Anxiety state	53	53
52	Noncardiac chest pain and alleged paroxysmal nocturnal dyspnea since chest wall injury 2 years ago; BP 165/100 mm. Hg; no EH; chest x-ray film negative; vital capacity 4 liters, 95% of normal; Decholin time 13 seconds	HVD	56	56

BBB = Bundle branch block
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ARF = Acute rheumatic fever
RHD = Rheumatic heart disease
CHD = Congenital heart disease

arrested minimal tuberculosis once each. An anxiety state, either unrelated or related to the knowledge of the presence of an electrocardiographic anomaly, occurred 11 times in the 33 patients without cardiac disease. This is not an unusual incidence of anxiety state, considering that the clinic chiefly serves applicants for a pension.

TABLE III.

FIRST DIAGNOSED AT AGE	LEFT BBB	RIGHT BBB
20–30	1	4
30–40	4	5
40–50	2	4
50–60	7	20
60–71	3	2

Cases Diagnosed Under the Age of 40.—
4 with heart disease
1 without heart disease
1 with heart disease
8 without heart disease

Of the Total 33 Without Heart Disease.—
9 diagnosed under age of 40
24 diagnosed over age of 40

Of the Total 19 With Heart Disease.—
5 diagnosed under age of 40
14 diagnosed over age of 40

Of the group without cardiac disease, only 10 had had available previous electrocardiograms. All had shown bundle branch block, and the presence of this abnormality had been known for more than 2 years in 6 cases. Ten of the 19 patients with cardiac disease had had available previous electrocardiograms, and all of these had organic heart disease at the time of the discovery of bundle branch block.

To summarize, of the entire group of 52 patients with bundle branch block 33, or 63 per cent, had no evidence of organic cardiac disease; 7 of these had left bundle branch block, and 26 had right bundle branch block. Of the 19 with disease of the heart, 10 had left bundle branch block, and 9 had right bundle branch block.

DISCUSSION

Most early workers felt that bundle branch block was a serious prognostic sign. When this applies to patients hospitalized because of obvious cardiac illness, it may be true. Soon it was recognized that the prognosis of bundle branch block was not so gloomy and depended upon the severity of the underlying cardiac disease. Still, little attention was paid to the possibility of the existence of bundle branch block without cardiac disease.

However, Graybiel and Sprague[3] mentioned "the few cases of functional or intermittent bundle branch block." Master, Kalter, Dack, and Jaffe[4] also mentioned "the occasional case in which a functional type of block occurs in normal hearts." Perera, Levine, and Erlanger[5] stated "some have no objective or subjective evidence of heart disease other than bundle branch block."

Although White[6] made no mention of patients without organic disease other than patients with transitory changes, he did state that the patients fall into 2 groups, 1 with a poor prognosis and another with a considerably better outlook. In the latter group, he said, the bundle branch block is likely to be the only evidence of cardiac disease, and right bundle branch block is more common than left bundle branch block.

TABLE IV. PATIENTS KNOWN TO HAVE BBB PRIOR TO CURRENT EXAMINATION

CASE NO.	WITH HEART DISEASE		DURATION (YEARS)	AGE AT CURRENT EXAMINATION
		Left BBB		
7	Angina, EH, failure	ASHD	10	44
8	Angina, infarct	ASHD, HVD	4	64
25	EH, failure	HCVD	2	62
27	Infarct	ASHD	4	23
31	Failure, EH	HCVD	1	49
35	Failure, EH	Unknown	7	46
44	Angina	ASHD	8	45
	5 out of 10 left BBB with heart disease known for more than 2 years.			
		Right BBB		
4	Probable infarct	ASHD	1	57
22	EH, multiple infarcts, gallop	ASHD	3	48
38	Angina	ASHD, HCVD	3	54
	2 out of 8 right BBB with heart disease known more than 2 years.			
		WITHOUT HEART DISEASE		
18		L BBB	11	58
40		R BBB	1	32
2		R BBB	1	56
3		R BBB	5	32
5		R BBB	3	25
6		R BBB	4	27
30		R BBB	6	40
37		R BBB	2	32
41		R BBB	5	46
12		R BBB	1½	44
	6 out of 33 patients without heart disease were known more than 2 years.			

Levine[7] stated, "It always denotes some disease of the myocardium," but he added, "There are instances of this (right bundle branch block) type in which there seems to be very little other evidence of organic disease and the prognosis may be extremely favorable." Six tracings with bundle branch block are shown in his book, and 2 of them are from patients who seem to be without cardiac disease. One, like some of the cases in the present series, came to attention because of 1 fainting spell, and the other developed the anginal syndrome only

after being observed for 14 years. More recently Levine stated[8] that such cases are not infrequent.

Willius, Dry, and Reeser[9] in reporting on more than 1,000 cases of disturbed intraventricular conduction wrote at length of a "wide S" group which is identical with right bundle branch block in the present terminology. This finding was compatible not only with a better prognosis than that offered for left bundle branch block patients and right bundle branch block patients with right axis deviation, but in more than 40 per cent of them there was nothing suggestive of cardiac disease other than the electrocardiogram.

Wood, Jeffers, and Wolferth[10] analyzed 64 cases of right bundle branch block. Twenty-five of these patients had no evidence of organic cardiac disease. Only 3 of the 25 were diagnosed under the age of 40 years. In 3 of their patients right bundle branch block appeared under observation, twice in association with definite coronary arteriosclerosis and once without any symptoms or signs. In 3 patients right bundle branch block appeared and disappeared from time to time. These patients had no signs or symptoms of cardiac disease. The pattern was found to be more common in a group of business executives over 45 years than in a group of unselected college students.

Von Deesten and Dolganos[11] reported right bundle branch block in 5 men ranging in age from 49 to 79 years, only 1 of whom had hypertension, and all of whom had been followed for more than 2 years, 1 for 11½ years, another for 8 years. None had any evidence of cardiac disease.

Langley, Reed, and Utz[2] analyzed 100 cases of bundle branch block seen in 6,900 patients who had had electrocardiograms in a naval hospital. Forty-four had right bundle branch block, 39 had left bundle branch block, and 17 were not classified because of the absence of multiple precordial leads. Twenty-nine of the patients had no organic cardiac disease, and 18 of these were individuals with right bundle branch block. Forty-four per cent of the patients without organic disease were under 40 years of age.

Gober and Sloan's[12] 118 cases of bundle branch block included 41 with right and 78 with left bundle branch block. Eighty had arteriosclerotic heart disease with or without hypertension, and 13 had no organic cardiac disease. Of the 54 patients alive at the time of the study, 41 had been known to have bundle branch block for 7 years or longer.

In a later report[13] White's group analyzed 281 patients with right bundle branch block. Of these, 93 were classified as being of undetermined etiology; this group included 5 patients with cor pulmonale and 1 with idiopathic myocardial hypertrophy, the remainder being thought to have "asymptomatic coronary disease." This group had a distinctly better prognosis than those with hypertensive, rheumatic, congenital, or definite arteriosclerotic disease. It is of interest that in the 52 cases reported in the present study, 9 with and 5 without definite cardiac disease were diagnosed under the age of 40 years. By comparison, in White's group of 281, only 14 were diagnosed before the age of 40 years.

It has been suggested that the patients without obvious organic cardiac disease and with bundle branch block may be in a latent phase and may have

other obvious manifestations at a later date.[13] Certainly, no completely definite statements about the patients presented herein should be made, but one is left with the choice of thinking that there is a group of patients with bundle branch block without significant cardiac disease or that there is a group of patients who have bundle branch block as an isolated manifestation of cardiac disease which only later manifests itself in other fashions. In regard to this, it may be remembered that in most patients with bundle branch block with obvious disease the conduction disturbance is usually found some time after the appearance of definite symptoms. On the other hand, the various authors cited, who gave prognostic data, mentioned that in their groups with a good prognosis the bundle branch block was often the only finding suggestive of cardiac disease.

Against the hypothesis that bundle branch block may exist in a large group of persons without organic heart disease the opinion has been stated that the mere existence of this electrocardiographic pattern presupposes a focal myocardial lesion, usually fibrosis, interrupting conduction.

This opinion does not seem to be necessarily true. Yater[13] found by means of his careful study of serial sections that often there was only diffuse fibrosis without a focal lesion, and that in a patient who had shown block in one of the branches there might be less damage on that side than on the other. Master[4] reported that in 100 patients with bundle branch block, almost all of whom had gross cardiac enlargement, the type of block was determined not by the presence of a focal lesion but by which ventricle was preponderantly enlarged. He stated that the disturbance was due merely to the lengthening of the pathway by the enlargement, except in the occasional case in which a "functional" type of block occurs in normal hearts.

Cases have been reported, for instance, by Vesell[14] and by Eichert,[15] in which bundle branch block has been a transitory phenomenon, both in the presence of and in the absence of definite organic disease. The change from normal mechanism to bundle branch block occurred in 1 case when the heart rate rose above 75, in 1 case when it fell to 40, in 1 case when it rose to 120 as from exercise, amyl nitrite, or atropine, and in 1 case in association with fright stimuli.

One case in the present series (Case 46) showed typical complexes of right bundle branch block alternating with normal mechanism without irregularity or change in rate. Two tracings were made on this patient during the same afternoon and both showed similar findings. This patient had no other evidence of cardiac disease.

Such occurrences as these are not compatible with the presence of a clinically significant organic focal lesion. It is clear also that in the case presented herein the presence of the complex showing bundle branch block is not dependent upon diffuse fibrosis, disproportionate ventricular enlargement, or unilateral ventricular strain. It is possible that a mechanism, possibly physicochemical, similar to that operative in these transitory cases, may be responsible in the permanent bundle branch block cases without an obvious trigger factor.

Four of the patients without evidence of clinically significant cardiac disease now have deeply rooted psychic disturbances which are due to their knowledge of the presence of bundle branch block and to the interpretation placed upon this

finding by their physicians. These crippling cardiac neuroses were precipitated by improper clinical evaluation and need not have occurred. Disease of the heart should not be diagnosed, whether bundle branch block be present or not, except with the criteria used in this study and in the presence of certain metabolic disorders and deficiency states.

SUMMARY

The occurrence of bundle branch block in the absence of definite organic heart disease has been regarded as a rarity. On the other hand, it has been well recognized that some cases of bundle branch block, especially if the right branch is involved, carry an excellent prognosis. The present study includes several patients known to have had a bundle branch disturbance for a number of years without suffering any cardiac disability. They have developed no other objective signs of cardiac disease, and they should not be considered to have clinically significant cardiac disease. Only continued observation will determine whether or not the remaining individuals who now have bundle branch block without any other subjective or objective evidence of cardiac disease may be placed permanently in the same category.

CONCLUSIONS

1. Of 5,000 electrocardiograms, 52 showed bundle branch block.
2. Sixty-three per cent of the patients with bundle branch block had no clinically evident cardiac disease.

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A VECTORCARDIOGRAPHIC ANALYSIS OF THE RSR′ COMPLEX OF THE UNIPOLAR CHEST LEAD ELECTROCARDIOGRAM. III.

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SINCE the routine practice of recording a complete unipolar chest lead electrocardiogram has become widely adopted, a distinctive pattern appearing in leads from the right precordium has been observed sporadically in normal persons[1] and somewhat more frequently in those with myocardial disease or cor pulmonale. It has been found very commonly in those with congenital cardiac malformations which are associated with right ventricular hypertrophy, namely, interatrial septal defects,[2] pulmonary stenosis, Eisenmenger's complex, and the tetralogy of Fallot.

This pattern, seen in any leads from V_{R7} to V_2, is characterized by the appearance of an initial positive deflection (the r wave) followed by a negative deflection (the S wave), and, finally, a late, wide, or slurred positive deflection (the R′ wave) is written. The initial positivity is often small and may be of such low amplitude as to appear isoelectric and be detectable only by careful timing of the onset of the QRS complex. The deflection may also be equal to or greater than the R′ wave. Its duration is from 0.01 to 0.03 second. The subsequent negativity may be marked, producing a deep S wave, or may merely produce a notch between the initial and final positivites. The slurred R′ wave and the late so-called "intrinsicoid deflection" in the leads from the right side of the chest are the distinctive features of the pattern.

The width of the QRS complex is found to range from 0.08 second to 0.16 second or more. The T wave is often diphasic or inverted. Leads from the left side of the chest (V_5, V_6, V_7) consist of a small q wave, a tall, narrow R wave, a shallow, wide, slurred S wave, and an upright T wave. The standard leads display a shallow, widened S wave in Lead I as the sole constant feature. Leads V_R or aV_R show either a primary and secondary positivity or a single, late R wave.

The most notable contributions to the elucidation of the genesis of this electrocardiogram have been made by Wilson,[3-6] and the pattern now bears his name. Electrocardiographic analyses[7-12] and studies of intracavity potentials[13,14] have added further information. Yet the significance has remained obscure, and a single lesion common to those without apparent heart disease and to those with the diverse pathological states displaying this cardiogram has not been

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identified. Analysis by means of spatial vectorcardiography was therefore undertaken in order to clarify these relationships and possibly throw some light upon the course of events.

Both in the electrocardiographic and vector descriptions to follow, these descriptive phrases which have been applied in the past to this type of electrocardiogram have been studiously avoided (complete or incomplete right bundle branch block, interventricular conduction disturbance, conduction delay, focal block, and "Wilson" block) because they imply certain specific abnormalities of the conduction system for which there is little direct proof and much dispute.

The vector analysis to be presented will be concerned merely with the description of two markedly different (QRS) vector loops each of which is capable of giving rise to the rSR′ complex described above. Moreover, one vector loop is constantly found in association with those congenital cardiac malformations which give rise to right ventricular hypertrophy. The other loop is seen in persons without known heart disease and in those with myocardial disease.

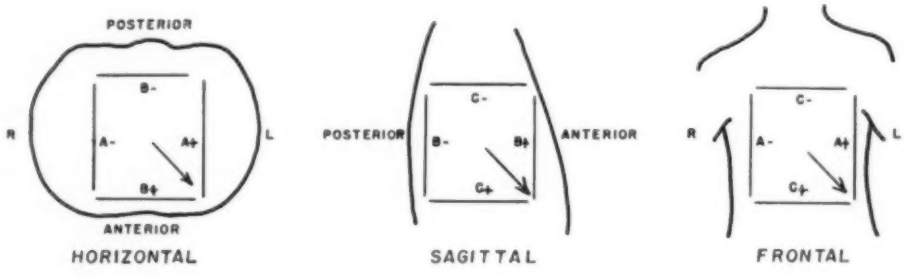

Fig. 1.—Diagram of electrode placement. Polarity of the three components, horizontal, sagittal, and vertical, as connected to the plates of the oscilloscope is indicated below.

The spatial vectorcardiogram records the instantaneous vector sum or balance of the electromotive field forces generated by the heart. As such, it has magnitude, sense, and direction. Electrocardiographic leads recorded from the surface of the body or extremities, bipolar or unipolar, are scalar projections of these spatially oriented forces, the latter along a line drawn from the point of exploration through the dipole. Unipolar chest leads are closely related to the horizontal projection of the spatial vectorcardiogram, at least in regard to direction and sense. This requires that they be regarded more as "semidistant" than as "semidirect" ones. They are regarded as "tapping" the horizontal projection of the vector rather than as representative of the potentials of the underlying musculature. This will be discussed in subsequent publications. Although an adequate correlation between unipolar chest leads and the horizontal vector projection is obtained, a very exact correspondence is not to be anticipated because the body itself is not a regular geometrical figure.

MATERIAL AND METHODS

The subjects were patients in the clinics and wards of The Mount Sinai Hospital. The patients who had congenital heart disease were all studied by

the authors, employing both fluoroscopy and phonocardiography. Angiocardiography and cardiac catheterization with intracardiac pressures and blood gas analysis were performed in all but one case. The other group of patients was also examined and fluoroscoped by the authors. From a considerably larger series, seven cases were selected for the present discussion.

A modification of the Duchosal and Sulzer[15] system of lead placement is used. This utilizes a cube figure representation of the trunk with electrode placement and polarity as shown in Fig. 1. The polarity is opposite to that used by Duchosal and so arranged that customary methods of vector analysis may be employed. The polarity of the bipolar lead has been selected so that impressed positivity (standardization) will move the beam to the right lower quadrant as seen by the observer. The frontal, sagittal, and horizontal plane projections of the vectorcardiograms are recorded simultaneously. The vector loop is interrupted 400 times per second by intensity modulation. Technique, apparatus, and theory have been discussed elsewhere.[16] Electrocardiograms are taken with a Technicon cardiograph at quadruple conventional speed (10 cm. per second) so that each heavy vertical line represents 0.05 second and each thin line 0.01 second.

I. CASES OF CONGENITAL HEART DISEASE WITH RSR′ PATTERN

CASE 1.—S. L., a 19-year-old white woman, had a clinical diagnosis of isolated pulmonary stenosis of a mild degree. A very loud systolic murmur associated with a systolic thrill was present over the second and third intercostal spaces to the left of the sternum. The heart did not appear enlarged. A slight prominence of the main pulmonary artery and increased convexity of the anterior border in the right anterior oblique view were the only significant roentgenological findings. Cardiac catheterization revealed a right ventricular pressure of 45/0 mm. Hg and 24/0 mm. Hg in the main pulmonary artery. The electrocardiogram (Fig. 2*A*) showed regular sinus rhythm, right axis deviation, and a QRS duration of 0.08 second. S_1 was slurred; a late R wave was present in V_R, an rsR′ complex in Leads V_{R3} and V_1, and an Rs configuration in V_6. The spatial vectorcardiogram is seen in Fig. 2*B* and discussed later with those of the remaining cases of this group.

CASE 2.—C. R., a 3-year-old female child, was believed to have Lutembacher's syndrome. A murmur was noted at 28 months of age. There had been one episode of unconsciousness. There was a short presystolic murmur at the apex, and a moderately loud systolic and early blowing diastolic murmur was heard just to the right of the apex. The heart was enlarged on fluoroscopic examination, and the pulmonary artery was large, showing increased pulsations. Cardiac catheterization revealed a right ventricular pressure of 39/3 mm. Hg and a pulmonary artery pressure of 20/6 mm. Hg. The electrocardiogram in Fig. 3*A* showed regular sinus rhythm, right axis deviation, a QRS duration of 0.07 second, a late R in aV_R, an rSR′ complex in V_{R3} and V_1, and an Rs in V_6. The spatial vectorcardiograms are shown in Fig. 3*B* and will be discussed further on.

CASE 3.—M. A., a 12-year-old white male child, was thought to have isolated pulmonary stenosis with interatrial septal defect. A murmur was noted at 6 months of age without associated symptoms. A loud, very harsh systolic murmur was heard at the base of the heart in the midsternal area, transmitted to the neck. There was a strong thrill in the second left intercostal space. Angiocardiography showed enlargement of the right atrium and ventricle and narrowing of the infundibular portion of the right ventricular outflow tract. Cardiac catheterization revealed a right ventricular pressure of 54/2.5 mm. Hg and pulmonary artery pressure of 12/5 mm. Hg. An interatrial communication was entered by the catheter. The electrocardiogram

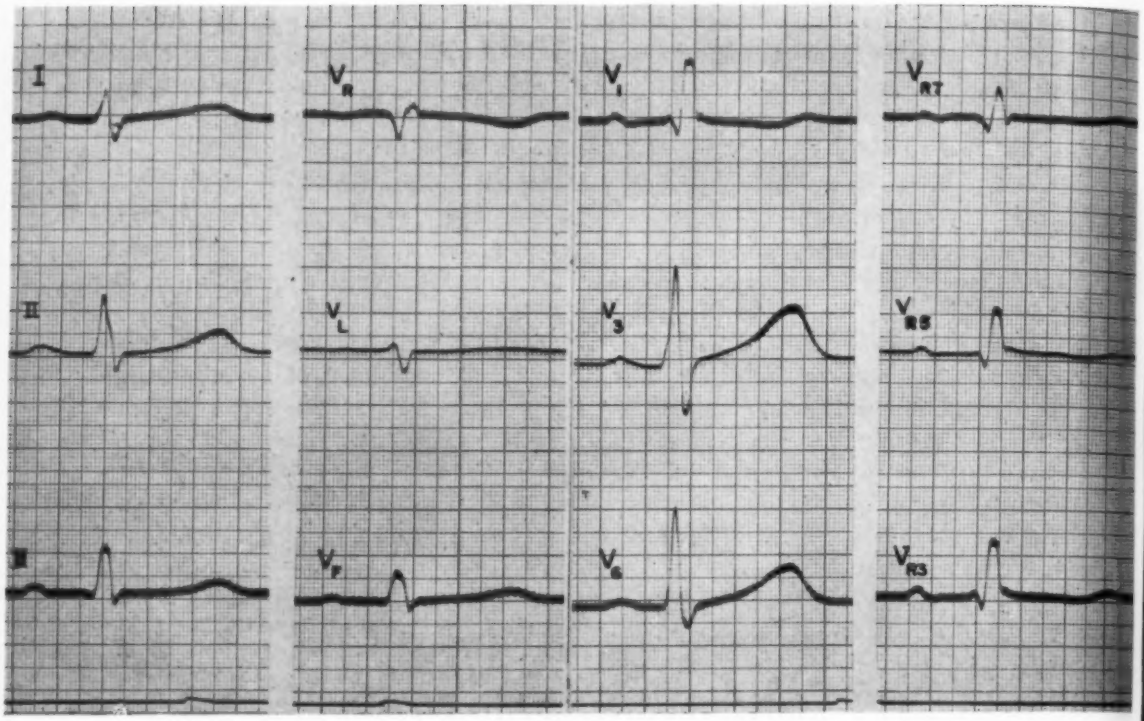

Fig. 2*A*.—Electrocardiogram of a 19-year-old woman (Case 1). Isolated pulmonic stenosis: rsR configuration of the ventricular complex in V_1.

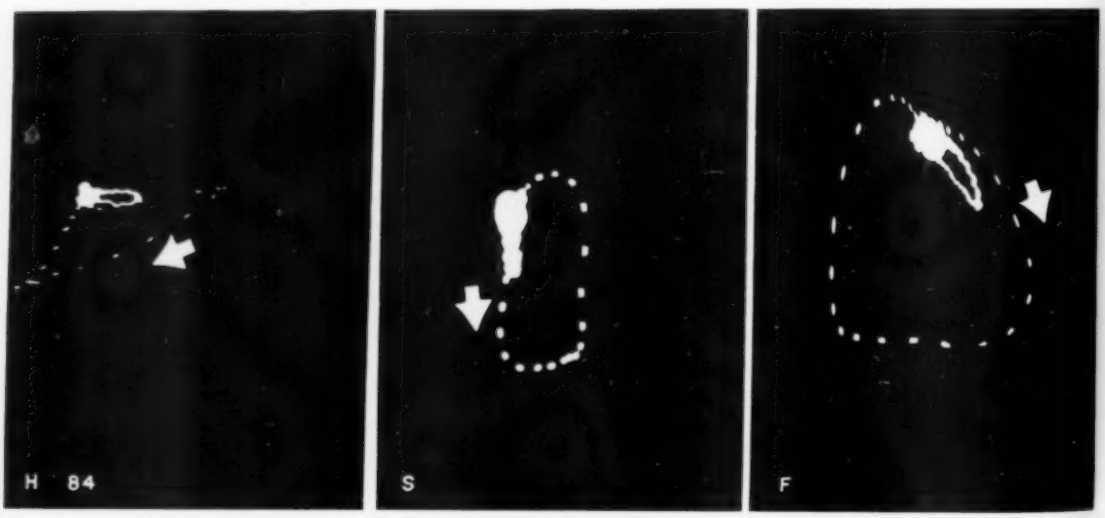

Fig. 2*B*.—Spatial vectorcardiogram. The frontal (*F*) and sagittal (*S*) projections denote right ventricular preponderance. The horizontal (*H*) projection, after a very brief forward orientation, deviates markedly to the left and then, in clockwise rotation, to the right.

in Fig. 4*A* showed regular sinus rhythm, right axis deviation, a QRS duration of 0.07 second, rSR′ in V_R, and a wide, notched R wave in Leads V_{R7} to V_{R5} and qRs in V_5. The vectorcardiogram is seen in Fig. 4*B* and is discussed later.

CASE 4.—P. M., an 11-year-old male child, was diagnosed as having interatrial septal defect without symptoms. A loud, harsh systolic murmur was heard along the left sternal border maxi-

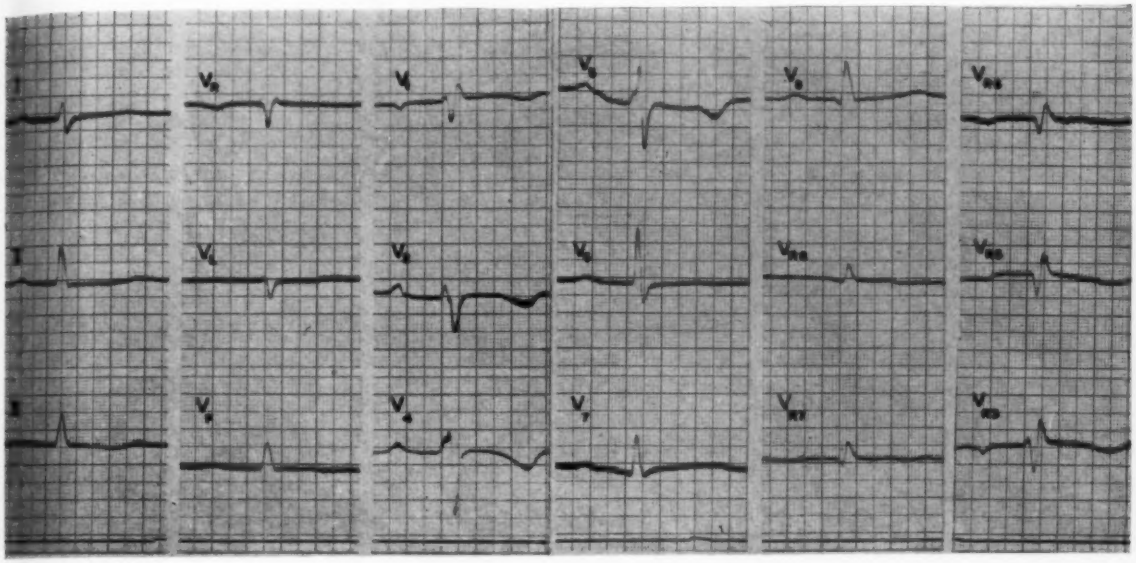

Fig. 3*A*.—Electrocardiogram of a 3-year-old girl with Lutembacher's syndrome. Unipolar chest leads recorded over V_1 and V_{R3} are of rSR′ configuration.

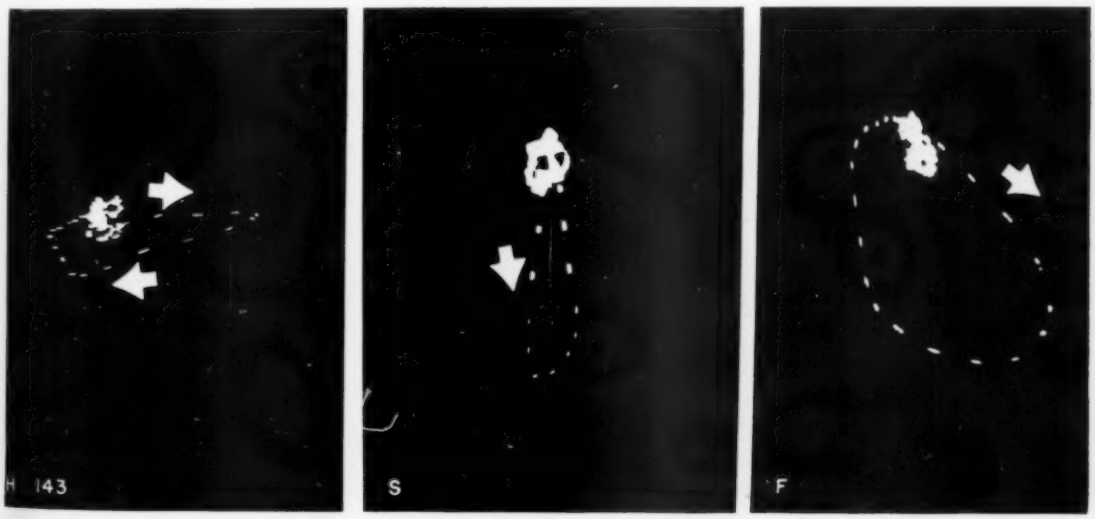

Fig. 3*B*.—The simultaneously recorded frontal, sagittal, and horizontal projections of the cardiac vector are indicative of moderate right ventricular preponderance. The horizontal loop (*H*) is initially oriented to the right and anteriorly, deviating sharply left posteriorly, and returning in clockwise rotation toward a right anterior rotation.

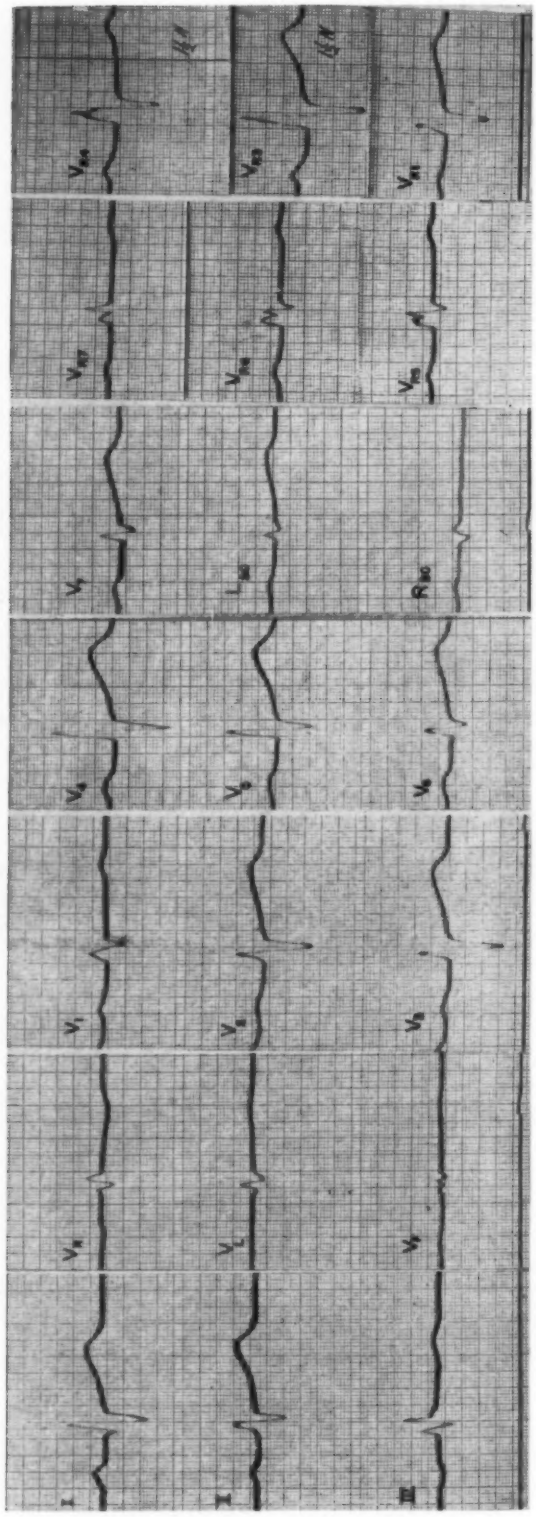

Fig. 4A.—Electrocardiogram of a 12-year-old boy with interatrial septal defect and pulmonic stenosis. Unipolar leads recorded over V_{R4-7} show an unusual type of RR' configuration.

mally over the pulmonic area. Angiocardiography showed dilatation of the right atrium, ventricle, and pulmonary artery. Cardiac catheterization showed a right ventricular pressure of 43/1 mm. Hg. The pulmonary artery could not be entered. The electrocardiogram in Fig. 5*A* showed regular sinus rhythm, right axis deviation, a QRS deviation of 0.08 second, a late R in V_R, and a transition from an rsR′ in V_{R5} to a notched, wide Rs in V_{R4} to V_1, and a qRs in V_6. The vectorcardiogram is seen in Fig. 5*B*.

CASE 5.—B. F., a 24-year-old white man with a diagnosis of interatrial septal defect, had a murmur noted at the age of 6 years, never associated with symptoms. A left precordial bulge was present. A moderately loud systolic murmur was heard at the third and fourth intercostal spaces at the left sternal border, followed by a soft diastolic murmur. Fluoroscopy revealed a normal-sized heart without significant chamber enlargement and marked dilatation, particularly of the left pulmonary artery which pulsated vigorously. The electrocardiogram seen in Fig. 6*A* showed regular sinus rhythm, right axis deviation with a wide, slurred S_1, a QRS duration of 0.11 second, a late R in V_R, an rsR′ complex from V_{R5} to V_1, and a qRs in V_6. The vectorcardiogram is seen in Fig. 6*B*.

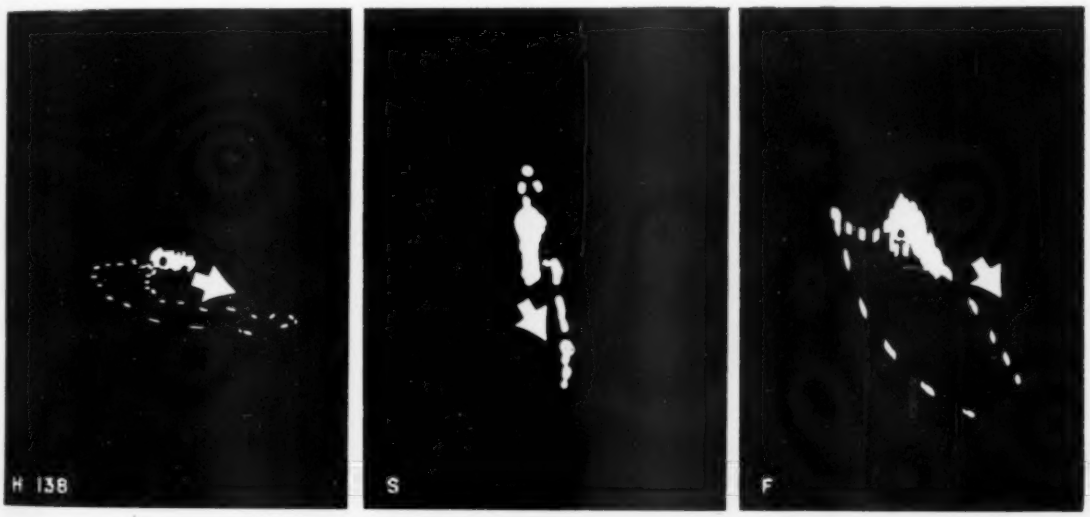

Fig. 4*B*.—The spatial vectorcardiogram reveals in its horizontal projection an initial anterior, then lateral, and finally right anterior orientation.

Comment on the Vectorcardiograms.—Two normal vectorcardiograms are included in Figs. 7*A* and 7*B*. Frontal and sagittal projections of vectorcardiograms have been described[15,17,18,19] and will be reported later. The frontal loops will show clockwise or counterclockwise rotation, according to the position of the main axis, with a slow initial invasion, a rapid component, and a short, slow terminal phase. The loops are smooth, regular in outline, follow a simple pathway, and show no areas of unexpected irregularity or slowing. The T-wave loops lie closely along the line of the longest diameter of the QRS loop. There may be a considerable variation in form and orientation, depending upon body build, cardiac rotation, and so forth. The horizontal projections of normal vectors run counterclockwise. The initial vectors, presumably the result of septal depolarization, point to the right, anteriorly, and upward and, therefore, project positively upon the line drawn from the approximate position of V_1 to the isoelectric center

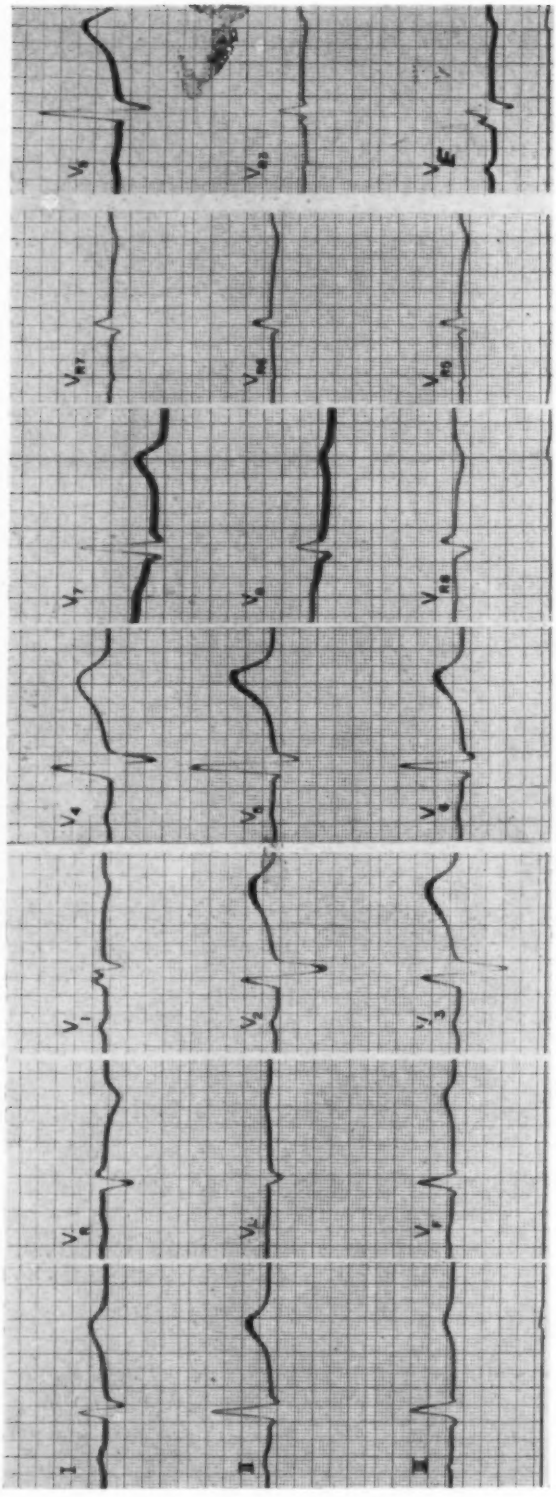

Fig. 5A.—Electrocardiogram of an 11-year-old boy with interatrial septal defect. rsR′ configurations are recorded over $V_{R5,6}$.

of the vectorcardiogram. This initial positivity produces the initial R wave of the scalar electrocardiogram at V_1 and conversely a q wave at V_6. The loop is then found to be directed to the left and laterally and finally to return posteriorly toward the point of origin.

The vectorcardiograms of the five patients who had congenital heart disease were likewise smooth, rounded, regular, and without regions of abnormal slowing. The frontal plane vectorcardiograms were all very similar and ran clockwise. The sagittal component ran counterclockwise in three (Figs. 2*B*, 3*B*, and 6*B*), clockwise in one (Fig. 5*B*), and was indeterminate in the other (Fig. 4*B*). The horizontal vectorcardiograms were all strikingly similar, and their analysis revealed the mechanism by which the rSR′ complex was produced. This is demonstrated in Fig. 12. As in the normal tracing, the initial vectors were directed anteriorly, to the right, and upward. This gave rise to the r wave. The centrifugal limb then turned more than 90 degrees counterclockwise and developed

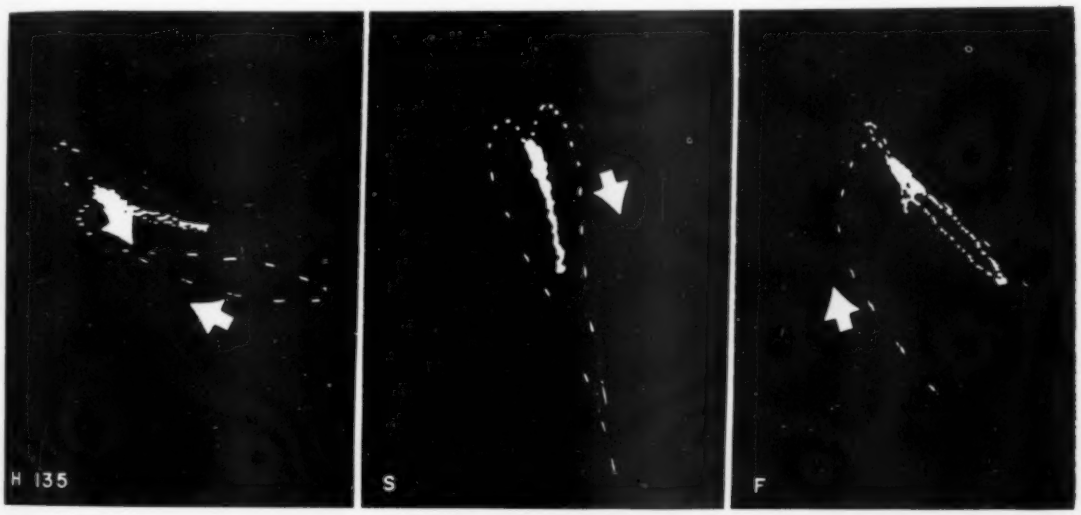

Fig. 5*B*.—Spatial vectorcardiogram. The horizontal projection shows an initial right anterior, then lateral, and terminally a right posterior orientation.

rapidly in normal fashion downward and to the left. This, as can be seen, was projected negatively along the line from the V_1 electrode to the center and produced either a deep S wave or a deep notch, depending upon its orientation and relative voltage. The loop then made a 160 to 170 degree clockwise turn to become the centripetal limb. Herein lay the difference from the normal. Unbalanced forces developed anteriorly, and the centripetal limb therefore swung anteriorly, upward, and to the right. This again resulted in positivity at the V_1 electrode and an R′ wave was written.

Two vectorcardiograms are included of two patients with what is considered unequivocal electrocardiographic evidence of right ventricular hypertrophy (Figs. 8*A* and 8*B*). The first had pulmonary stenosis with an interatrial communication and a right ventricular pressure of 90/0 mm. Hg. The second had tetralogy of Fallot with marked enlargement of the right ventricle.

The electrocardiogram of the first patient (Fig. 8*C*) showed right axis deviation, a QRS duration of 0.07 second, and an Rs type of complex in leads from the right side of the chest and qR in those from the left. The second patient showed right axis deviation, a QRS duration of 0.08 second, a notched, tall R in Leads V_{R6} to V_2, and a qrS in left-sided chest leads (Fig. 8*D*). The vectorcardiograms were similar to those of the rsR′ group. The initial, small segment of the loop occupying the first 0.01 to 0.03 second was directed anteriorly and to the right in both groups. The centrifugal limb, in this latter group, however, was directed

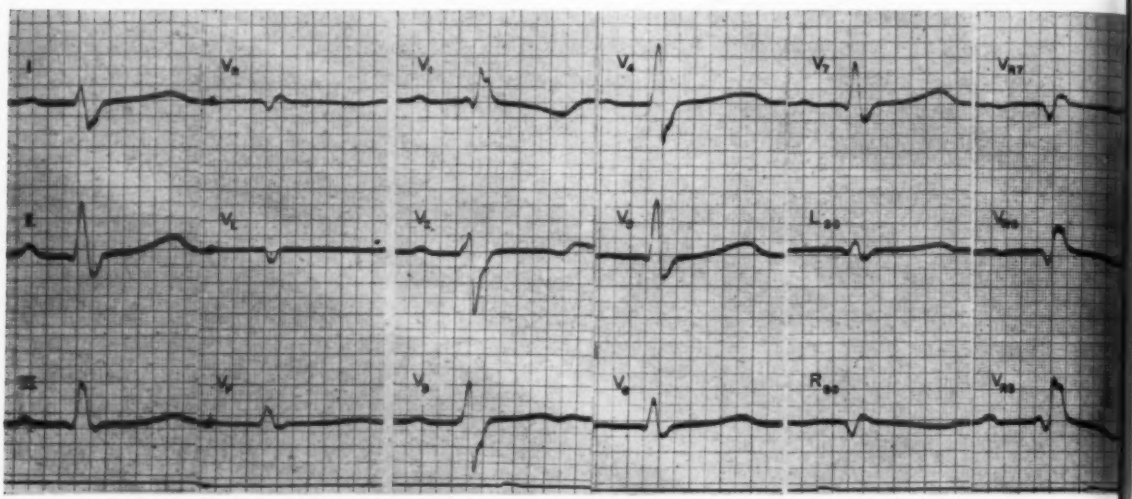

Fig. 6*A*.—Electrocardiogram of a 24-year-old man with interatrial septal defect. rsR′ configuration of the QRS complexes is seen in V_1 and V_{R2}.

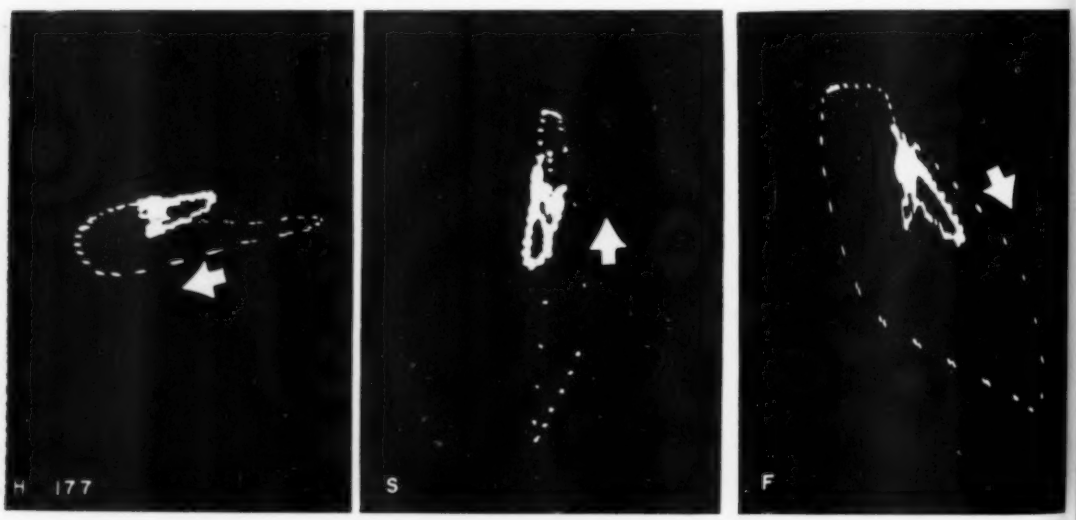

Fig. 6*B*.—Spatial vectorcardiogram. The initial orientation of the horizontal loop is right anteriorly, turning to the left and again right anteriorly in its terminal phase.

toward the left for only a short time. The potential forces which directed this vector pathway to the right and anteriorly developed much earlier than they did in the previous cases. The only difference then between the two groups is that the orientation of forces directed to the right and anteriorly occurred more rapidly and was of greater magnitude in this latter group. Since the fundamental vector pathway and characteristics were similar in both of these groups, one might infer that they were generically similar and assume that all degrees of transitional

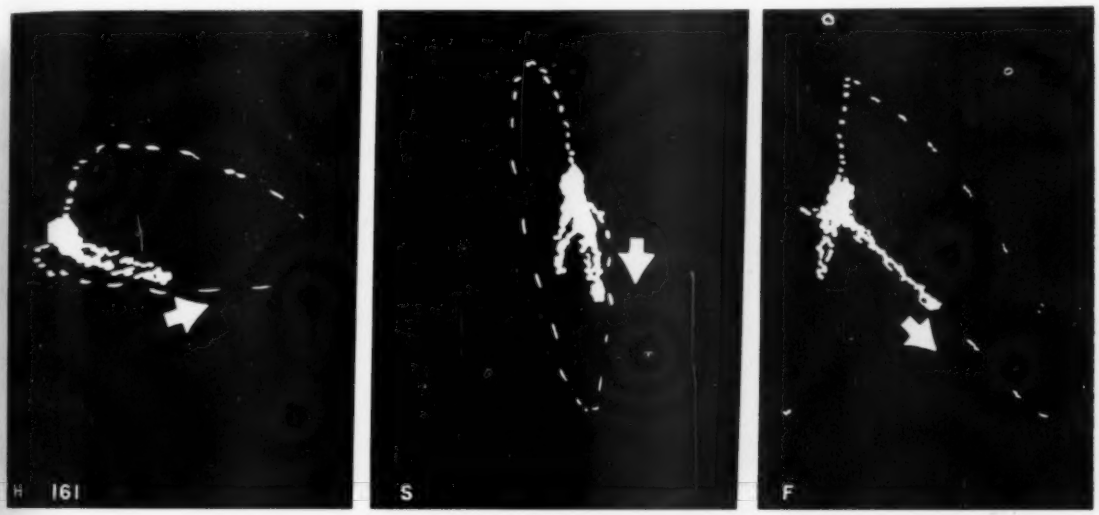

Fig. 7*A*.—Normal spatial vectorcardiogram. The frontal and horizontal projections reveal counterclockwise rotation.

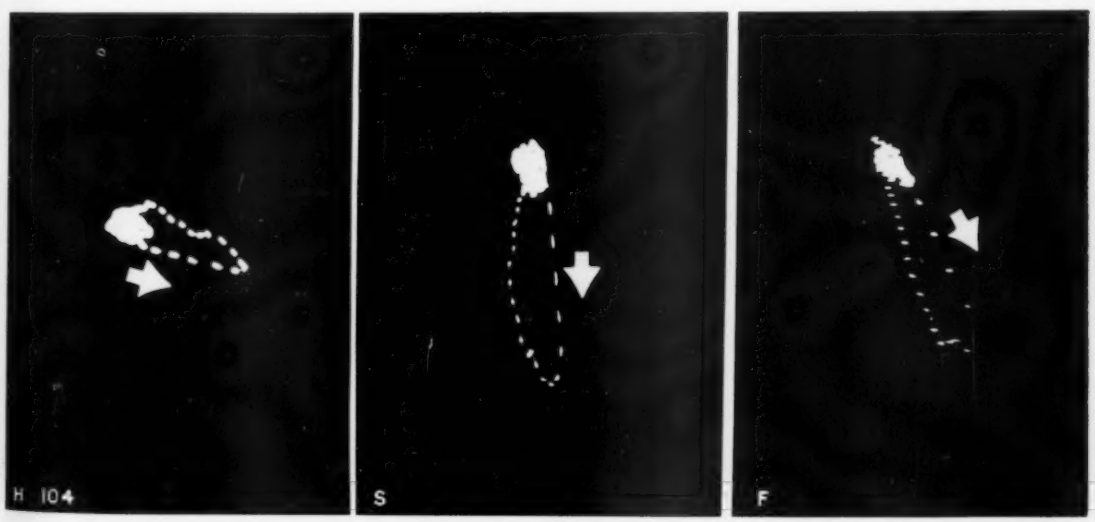

Fig. 7*B*.—Normal spatial vectorcardiogram. Counterclockwise rotation of the horizontal projection is associated with clockwise rotation in the frontal projection.

forms exist between those vectorcardiograms associated with the rsR′ complex and those of classical right ventricular hypertrophy. This will be discussed in subsequent publications. There is, likewise, a roughly correlated anatomical relationship of the same nature. The latter group was associated with considerably greater degrees of right ventricular hypertension than the former, and it seems reasonable to predict that the ratio of right to left ventricular muscle

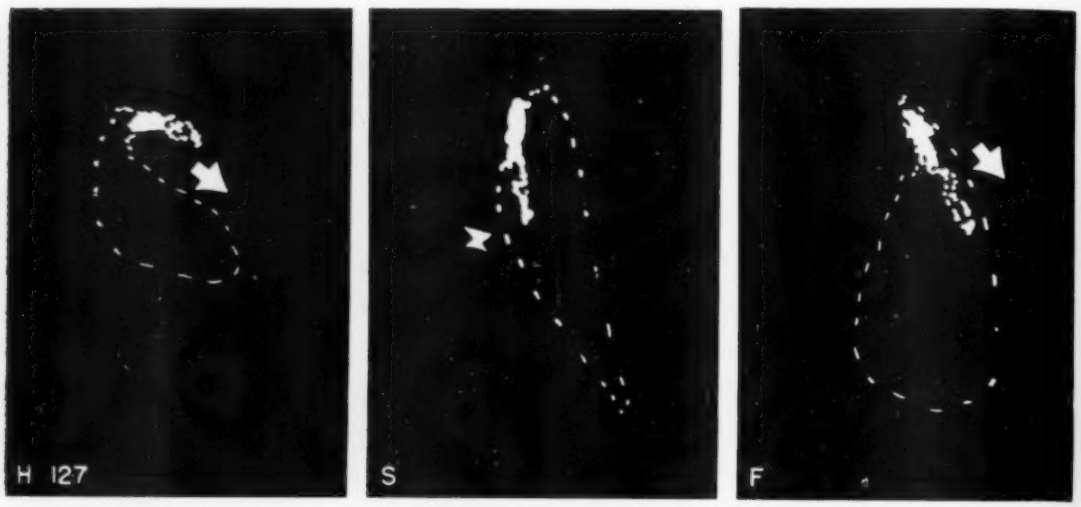

Fig. 8*A*.—Interatrial septal defect and pulmonic stenosis. Right ventricular pressure 90/0 mm. Hg. Spatial vectorcardiogram shows an essentially right anterior orientation. The serpentine course of the initial loop is the cause of the slow and slurred upstroke of the R wave in V_1 and V_{R3}. The sagittal projection has a clockwise rotation.

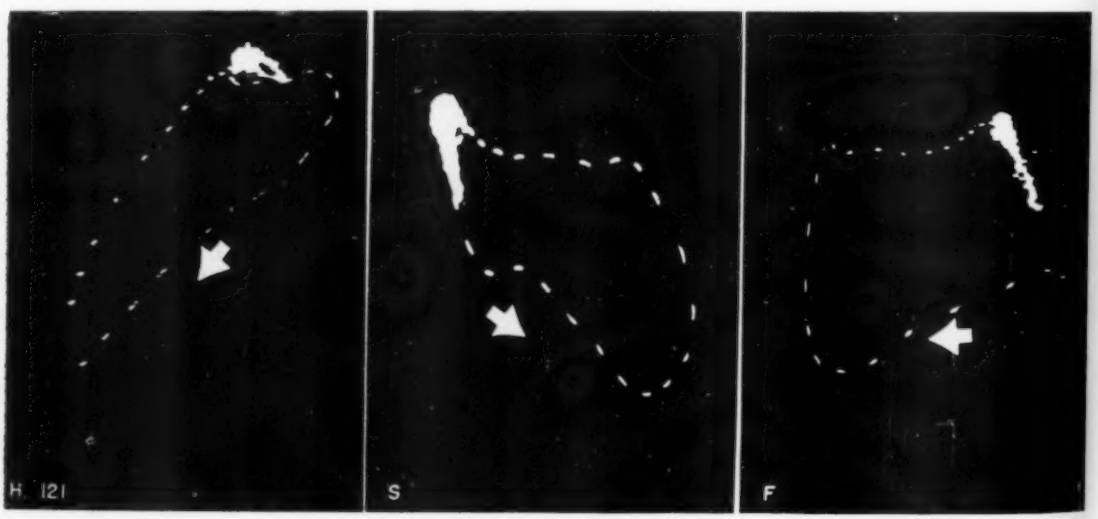

Fig. 8*B*.—Tetralogy of Fallot spatial vectorcardiogram. The horizontal projection shows a right anterior, then a brief left posterior, and finally a predominant right anterior orientation.

mass was greater in this group than in those with interatrial septal defects having lower right ventricular systolic pressure.

In summary, then, vector analysis indicates that the rsR′ pattern found in patients with congenital heart disease is a variant of the right ventricular hypertrophy pattern and is seen in those patients associated with a lesser degree of right ventricular hypertrophy than that giving rise to the classical pattern.

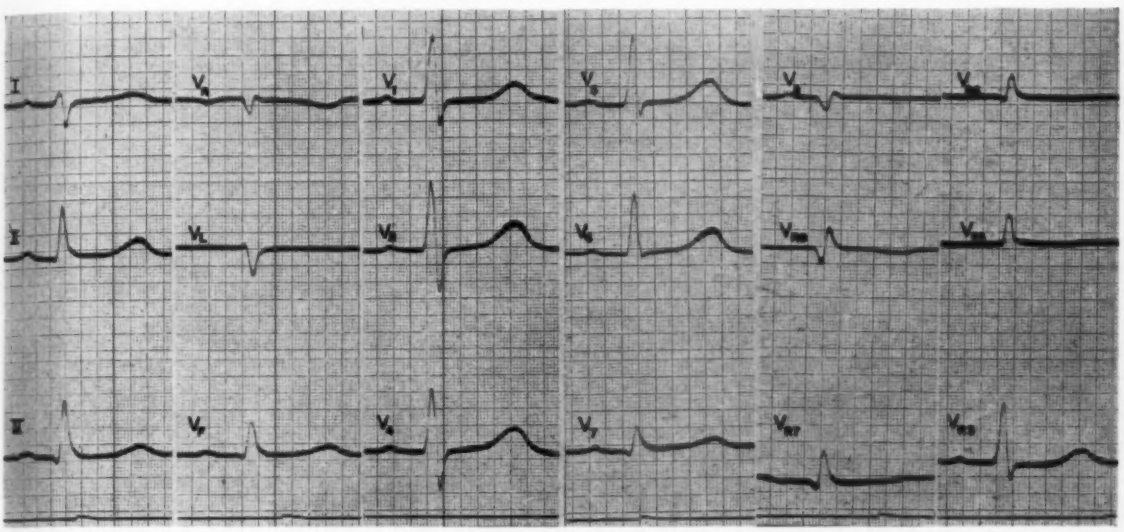

Fig. 8*C*.—Electrocardiogram corresponding to spatial vectorcardiogram 8*A*. Note the slurred upstroke of R in V_1 and V_{R3}.

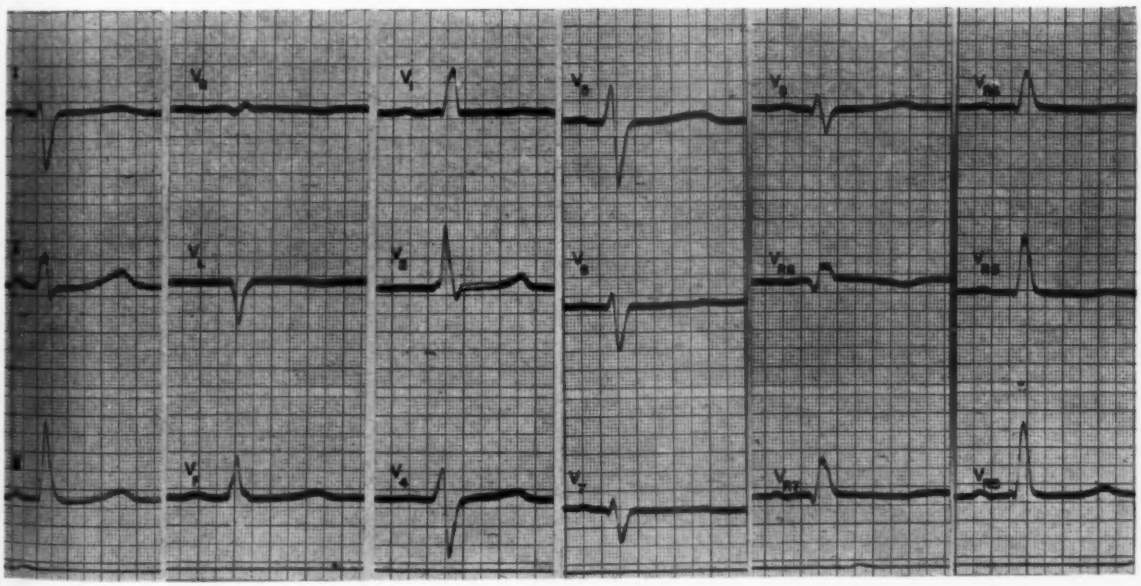

Fig. 8*D*.—Electrocardiogram corresponding to spatial vectorcardiogram 8*B*. Note the RR′ in V_1 and V_{R3} and the qrS in V_6 and V_7.

II. CASES NOT ASSOCIATED WITH RIGHT VENTRICULAR HYPERTROPHY

CASE 1.—L. Z., a 62-year-old white woman, had a history of essential hypertension of moderate degree for many years. Fluoroscopy revealed a mildly enlarged heart due to concentric left ventricular hypertrophy. The electrocardiogram (Fig. 9*A*) showed a regular sinus rhythm and a QRS duration of 0.12 second. There was a small q, tall R, and shallow, slurred, widened s wave in Lead I. There was a small r, deep S, and widened, low amplitude r′ in Lead III. V_R

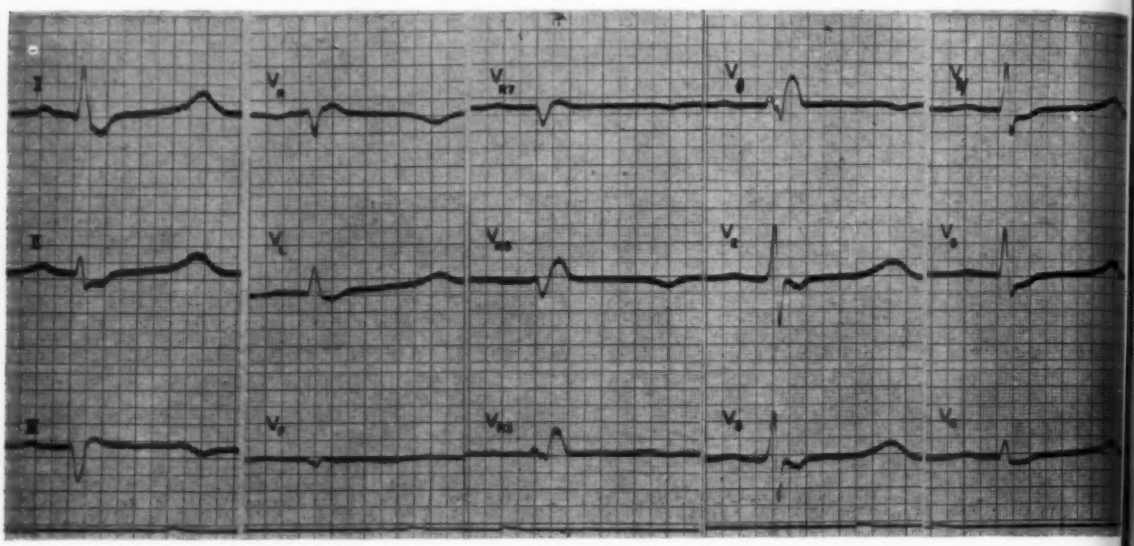

Fig. 9*A*.—Electrocardiogram of a 62-year-old woman with moderate hypertension for many years. An rsR′ configuration of the QRS complex in V_{R5}, V_{R3}, and V_1 was recorded.

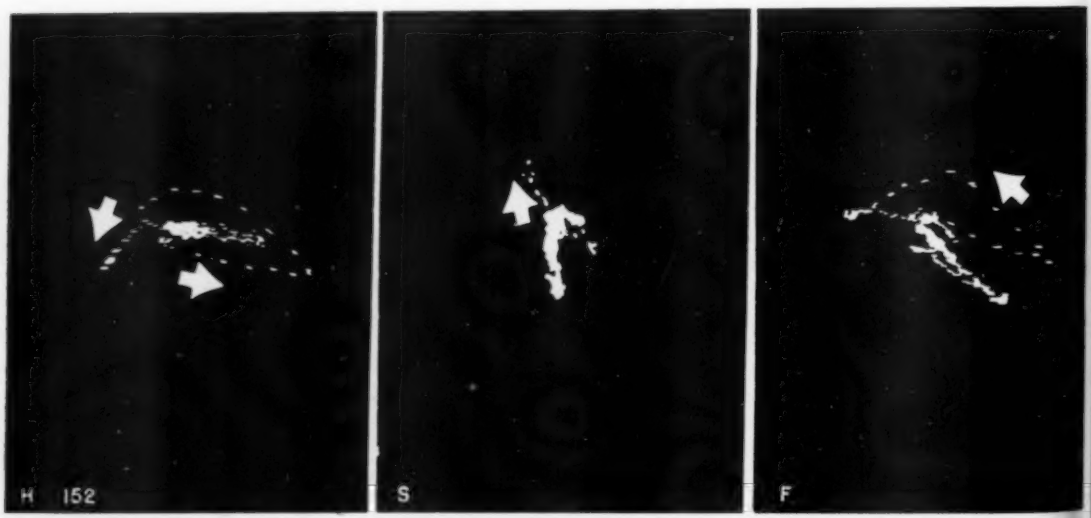

Fig. 9*B*.—Spatial vectorcardiogram. In the horizontal projection the initial loop has a normal direction and sense. The terminal portion has a marked right anterior orientation. The latter is characteristically found in the "Wilson" type of conduction defect.

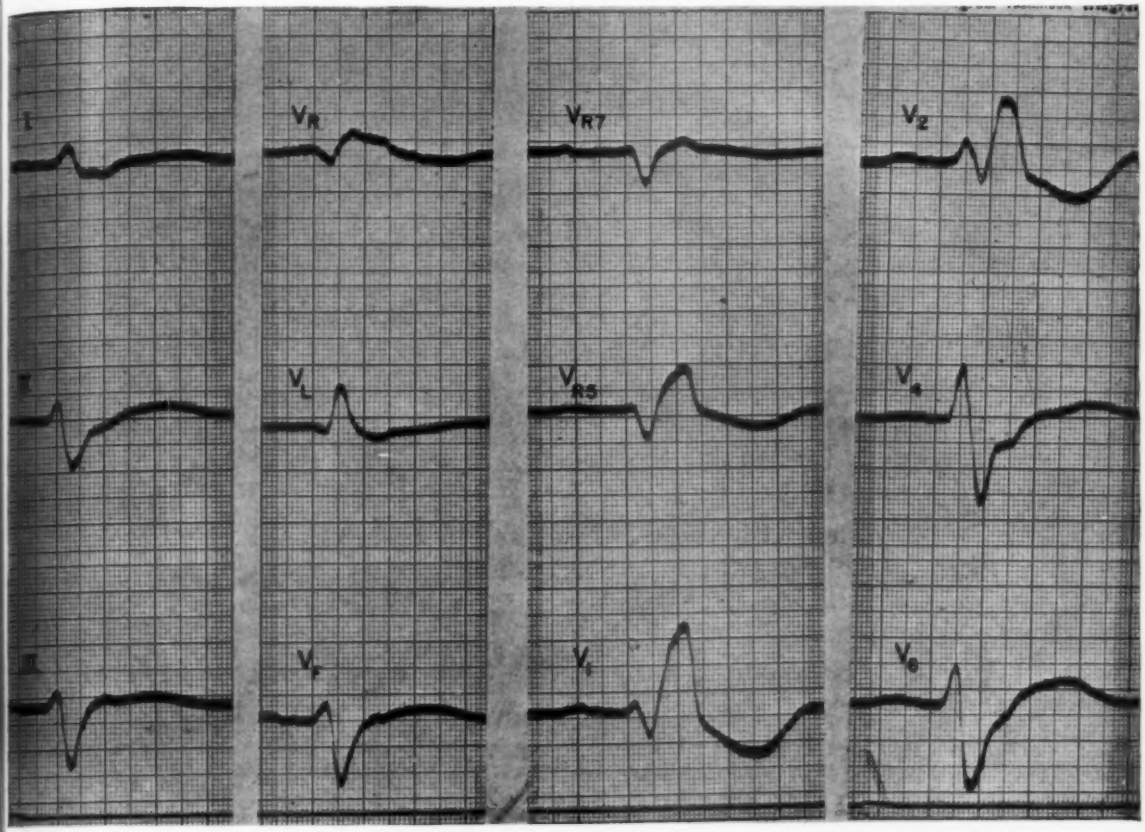

Fig. 10*A*.—Electrocardiogram of a 71-year-old man with sudden onset of severe congestive heart failure. rsR′ configurations are found from V_{R5} to V_2.

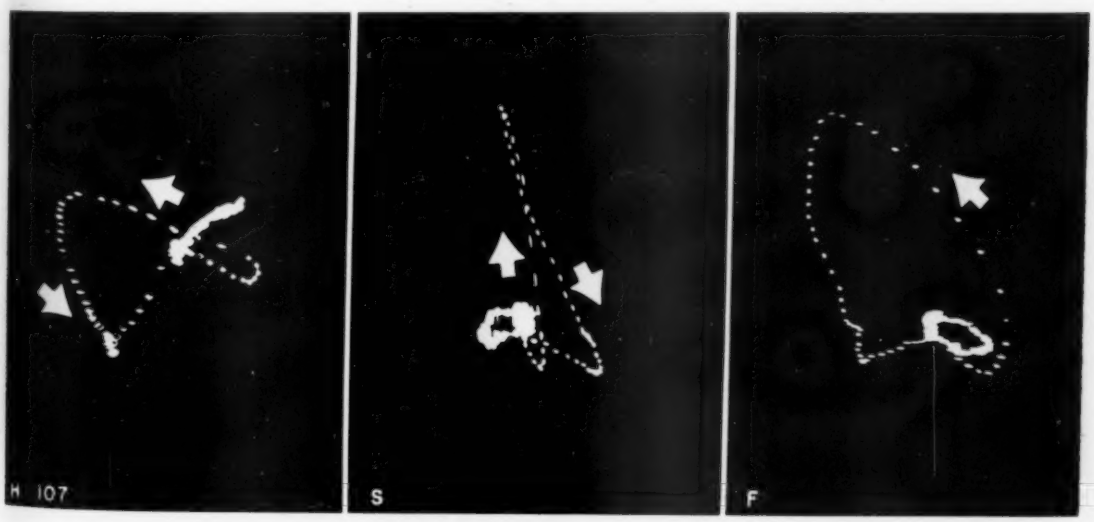

Fig. 10*B*.—The spatial vectorcardiogram reveals a markedly abnormal position of the major portions of the spatial loop (right laterally). Its terminal loop is again seen right anteriorly.

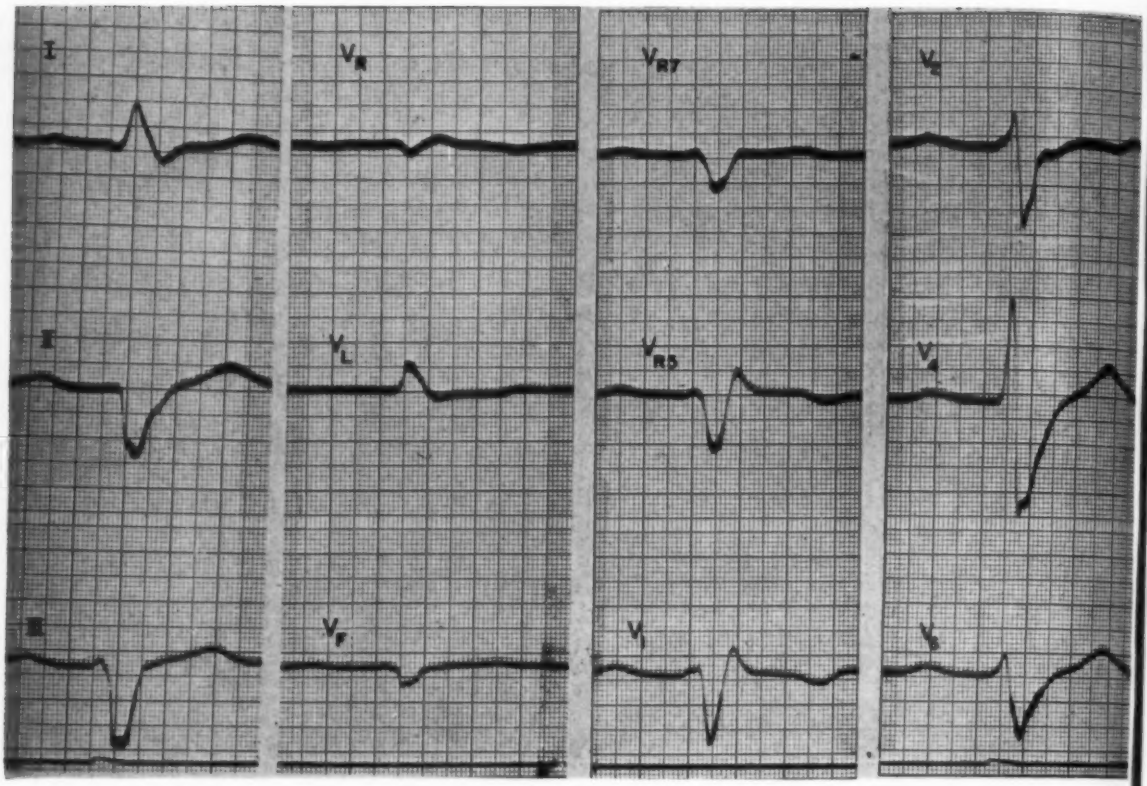

Fig. 11*A*.—Electrocardiogram of a 46-year-old man with marked hypertension and marked left ventricular enlargement for several years. An rsR′ pattern is recorded from V_{R5} to V_1.

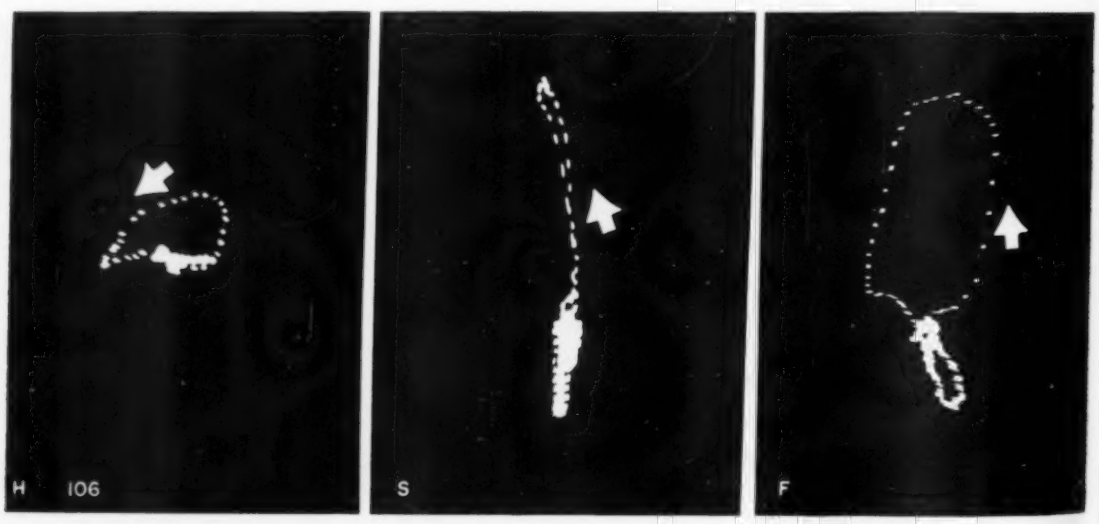

Fig. 11*B*.—Spatial vectorcardiogram. The main loop is oriented vertically, slightly posteriorly with a right, lower, anterior appendage.

showed rSR′ configuration. Precordial leads showed an rsR′ pattern in leads from V_{R5} to V_1. Lead V_6 consisted of a qR and a widened, shallow s wave. The spatial vectorcardiogram is seen in Fig. 9*B*.

CASE 2.—P. M., a 71-year-old white man, was operated upon for a carcinoma of the sigmoid and postoperatively went into sudden and severe congestive failure. There was no previous history of a coronary occlusion. Left ventricular enlargement of mild degree was noted on x-ray examination. The electrocardiogram (Fig. 10*A*) showed a QRS duration of 0.14 second. Standard leads showed a small r wave and a shallow, slurred s wave in Lead I and a small r, deep S, and low amplitude plateau r′ wave in Lead III. V_R showed a qR complex. The precordial leads from V_{R5} to V_2 showed an rsR′ complex, and V_6 consisted of a small r and a deep, widened S wave. The vectorcardiogram is seen in Fig. 10*B*.

CASE 3.—B. L., a 46-year-old white man, had marked hypertension for several years and fluoroscopic evidence of marked left ventricular hypertrophy and enlargement. The electrocardiogram (Fig. 11*A*) exhibited a QRS duration of 0.12 second. Standard lead I consisted of a small q, tall, widened R wave, and a shallow, widened s wave. Lead III consisted of a small r, deep, widened S wave, and short, isoelectric plateau. Lead V_R was of low amplitude and was diphasic. Leads V_{R5} and V_1 showed a QRS complex different from the previous cases in that the r and r′ were small and the intervening S wave deep and wide. Lead V_6 showed only a small r and deep, widened S waves. The vectorcardiogram is seen in Fig. 11*B*.

Comment on Vectorcardiograms.—These vectorcardiograms form a very heterogeneous group. They are markedly different in form from those associated with right ventricular hypertrophy, and they are markedly different from one another. There is no difficulty in distinguishing any one of these vectorcardiograms from any of those associated with right ventricular hypertrophy; nor is the difference merely a quantitative one of degree, such as is seen in the variations of the subgroups associated with right ventricular hypertrophy. The distinct qualitative difference in vector pathway and form permits the assumption that entirely different mechanisms are involved in the production of these similar scalar electrocardiograms.

These three vectorcardiograms have one characteristic feature in common which accounts for their similarity. The QRS vector loop, in its terminal portion, departed from the main loop and was directed sharply to the right and anteriorly forming a terminal "appendage." The loop at this point became markedly distorted and irregular, with its velocity markedly reduced. It is this slow and irregular terminal portion, whose orientation was to the right and anteriorly, which accounts for the increased QRS duration, for the slurred S wave in Lead I, the slurred late positivity in Lead V_R, and the late, wide, slurred R′ wave seen in the leads from the right side of the chest. The derivative electrocardiograms of the horizontal plane projections of the spatial vectorcardiogram are illustrated in Fig. 12.

Vectorcardiograms of this type have been known to characterize this form of electrocardiogram since the reports of Wilson and Johnston[18] in which two frontal plane vectorcardiograms similar to those reported here were published. A very extensive review, critical analysis, and vectorcardiographic study were made by Vastesaeger,[20] who used a somewhat different method of lead placement, but came to similar conclusions regarding the characteristics of this pattern. There is much difference of opinion as to whether this pattern represents true

right bundle branch block or merely a local abnormality of one of the secondary ramifications of the Purkinje system in the right ventricle.[15,20,21] Any extensive discussion of this problem is beyond the scope of the present paper.

A brief description of the major portion of the vector loop will serve to illustrate the great variety of forms which may coexist with an abnormal terminal "appendage." The rapid portion of the QRS loop presumably reflects potential forces produced predominantly by the left ventricle, and therefore it may assume any form, either normal or pathological.[20] The first vectorcardiogram, seen in

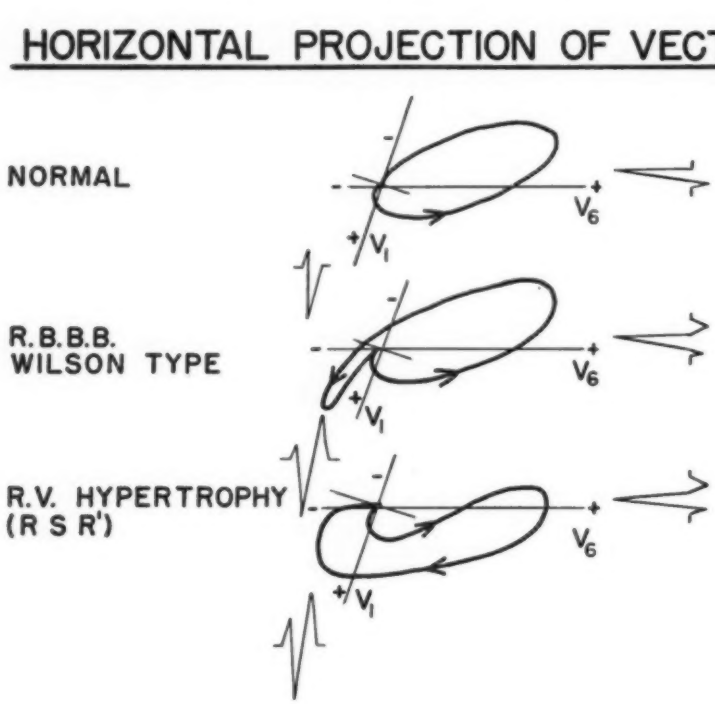

Fig. 12.—Diagrammatic vector analysis from horizontal vector projections for V_1 and V_6 unipolar chest leads.

Fig. 9*B*, is commonly found in patients with moderate left ventricular hypertrophy or a horizontal heart. The second vectorcardiogram is markedly abnormal, inasmuch as it was inscribed in the right upper anterior quadrant and progressed in a counterclockwise direction. This is an abnormal location and direction and suggests the presence of abnormal vectorial forces. The third vectorcardiogram, in its basic form, may be seen with marked left ventricular hypertrophy.

The characteristics of this group of cases not associated with right ventricular hypertrophy may be summarized by stating that the vector form and pathway are entirely different from those seen which were associated with right ventricular hypertrophy. The late positivity over the right precordium here is associated with the finding of a terminal abnormal deviation of the vector loop from its

expected pathway toward the right and anteriorly. This terminal segment is abnormal, not only in its deviation, but also in its irregularity and slow progression. The major portion of the vector loop seems to be unrelated to this terminal segment, and normal major loops as well as abnormal ones of any type may be observed in combination.

SUMMARY AND CONCLUSIONS

A study of the rsR′ complex observed in unipolar electrocardiograms over the right side of the chest has been conducted by means of an analysis of the spatial vectorcardiogram from its projection in the frontal, sagittal, and horizontal planes. This study indicates that:

1. Each of two markedly different QRS vector loops is capable of producing the RSR′ complex.
2. One of these QRS vector loops is seen constantly in patients with congenital heart disease associated with hypertrophy of the right ventricle.
3. The QRS vector loops of patients with classical electrocardiographic patterns of right ventricular hypertrophy are closely related to those seen in patients with congenital cardiac disease with RSR′ complexes. It is believed that the latter is a variant of the former.
4. QRS vector loops of those cases not associated with right ventricular hypertrophy are all characterized by a slow, irregular terminal loop directed to the right and anteriorly, which is probably the result of an abnormally slow, unbalanced development of vectorial forces. This accounts for the late positivity manifested in leads derived from the right side of the chest and results in the RSR′ type of complex seen in these patients.

The cardiac catheterizations were performed by Dr. F. King, Dr. A. Gordon, Dr. R. Borun and Dr. R. Lasser, New York, N. Y. The angiocardiograms were done by Dr. S. Brahms New York, N. Y.

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THE UNIPOLAR CHEST AND EXTREMITY LEAD ELECTROCARDIOGRAM IN CHILDREN (NEWBORN TO TEN YEARS OLD)

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THE first electrocardiogram in children was taken by Nicolai and Funaro in 1908. They recorded standard lead I only in forty-five infants and children and noticed frequently a deep S wave.[1]

The first investigation of precordial leads in children was carried out by Master, Dack, and Jaffe in 1935 in seventy-one normal children, 2 to 15 years old. They recorded seven precordial leads, each separated by a distance of 2 cm. at the level of the fourth intercostal space beginning at the right margin of the sternum. The most significant observation was that the T wave, initially negative, became positive in the proximity of the apex. In very young children the T wave often remained negative even at the apex. They also found frequent absence of P waves, a P-Q interval from 0.10 to 0.14 second, and QRS duration between 0.06 and 0.08 second; no RT deviations over 1 mm. were found in any position. It was noted that in children at age of 14 to 15 years the precordial electrocardiogram resembled that of the adult.[2,3]

In 1936, Rosenblum and Sampson recorded the electrocardiogram in fifty normal children, 1 to 16 years old. The chest-back lead and three precordial leads in the second, third, and fourth intercostal spaces at the left margin of the sternum were used. They found that the T wave was negative in 64 per cent, diphasic or isoelectric in 32 per cent, and positive in only 4 per cent. They compared these records with those of sixty-six normal adults in whom the T wave was positive.[4]

In the same year, Robinow, Katz, and Bohning recorded a single precordial lead in the fourth intercostal space at the left margin of the sternum. They found a negative T wave in 58 per cent of sixty-one children, 5 to 15 years old. They noted that the younger the children the greater the percentage of negative T waves and that in children about the age of 14 years the T wave was similar to that of the normal adult.[5]

In 1942, Groedel, Kisch, and Reichert studied the electrocardiographic changes in the standard and chest leads during the first stages of life. These investigators found a right chest electrocardiogram in all chest positions immediately after birth which changed within a few hours or several days to a left chest pattern in the left axillary region (CR_5), and the right chest lead (CR_1) showed a change in the R/S ratio—the amplitude of R increased and S decreased.[6]

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In 1944, Groedel and Miller studied electrocardiograms in the newborn infant. A right heart pattern was observed in chest positions 1 and 2 and a left heart pattern in positions 5 and 6, while positions 3 and 4 showed a mixture of the two.[7]

In 1945, Ash investigated 150 children, 9 to 15 years old. Six precordial leads were employed. She found that the R wave may be greater than the S wave near the sternum, or a double R may be observed in the same area. T-wave inversion or notching may be present. No Q wave was found in CF_2, nor was there a Q wave of more than 3 mm. present on the left side of the apex.[8]

In 1946, Battro and Mendy investigated the electrocardiograms of fifty healthy children who were divided into three groups: A (0 to 2 years), thirteen children; B (3 to 5 years), sixteen children; and C (6 to 10 years), twenty-one children. These investigators employed the standard leads (I, II, and III), three extremity unipolar leads, and six precordial unipolar leads in accordance with the specifications of the American Heart Association. The following are the characteristics observed in the three groups: Group A, predominance of R over S in V_1, frequency of negativity or diphasism of the T wave even up to V_6; Group B, tendency to isodiphasism of R and S to the right, negativity or diphasism of T up to V_6 although less frequently than in the former group; Group C, predominance of S over R in V_1 as in the adult, absence of negative T wave in V_5 and V_6, inversely to what was observed in Groups A and B.[9]

In 1950, Switzer and Besoain studied the electrocardiograms of fifty-two normal children, 1½ to 15 years old. They employed the usual standard leads, the aV limb leads, and nine precordial leads (V_{4R}, V_{3R}, and V_1 to V_7). These investigators confirmed the previous findings of increased rate, frequent sinus arrhythmia, and frequently notched, inverted, or diphasic T waves in the chest leads; a good-sized Q wave was frequently observed in Leads II, III, aV_F, V_4, V_5, and V_6. A small Q wave was infrequently found in V_3.[10]

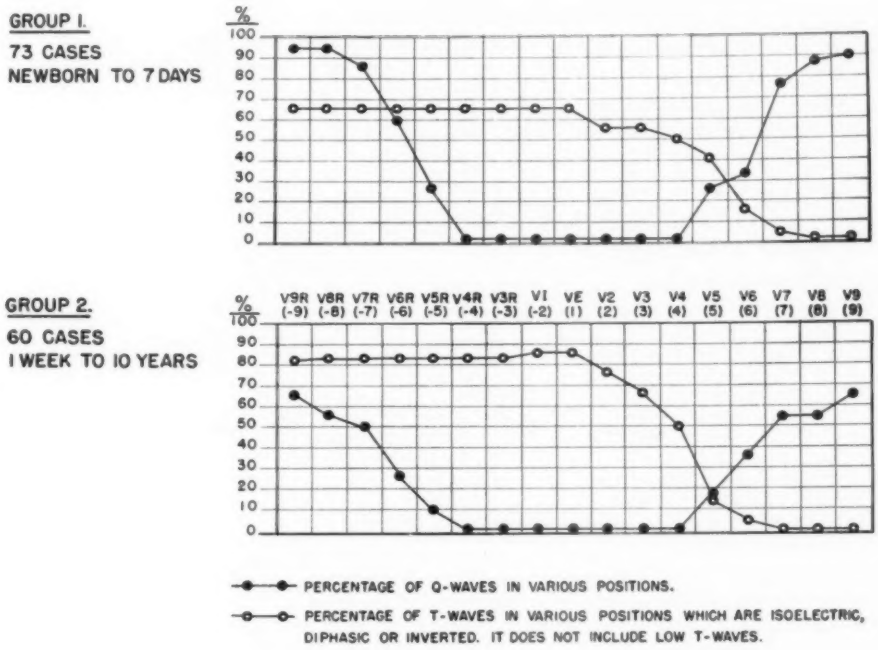
In 1950, Schaffer, Burstein, Marcia, Barenberg, and Stillman studied the unipolar electrocardiograms in fifty normal newborn infants. The three standard leads, augmented unipolar limb leads, V_{6R}, V_{4R}, $V_{STERNUM}$, and V_4 to V_6 were employed. The most significant observation was that the T wave was, as a general rule, inverted in leads on the right side of the chest and upright in the left chest leads.[11]

The objectives of the present investigation are (a) to study the multiple, circumferential, unipolar chest lead electrocardiogram in the newborn infant; (b) to compare these with similar electrocardiograms in older children; (c) to study the extremity leads in the newborn infant; and (d) to attempt to explain anatomically and physiologically the different electrocardiographic patterns.

MATERIAL

Our investigation was carried out on 133 children, seventy of whom were normal newborn infants from the maternity wards of the Beth-El Hospital in Brooklyn, N. Y., and sixty-three children from the pediatric wards of The Mount Sinai Hospital in New York. All these subjects had complete physical examinations, and some had roentgenographic studies of the chest and, as far as could be

determined, were free of cardiovascular disease. Some of the Mount Sinai Hospital cases (63) were admitted to the hospital for tonsillectomies or minor surgical operations and were free of any condition which is known to affect the heart, such as thyroid disease, anemia, rheumatic fever, and so forth. Our cases were divided into two groups: I. Newborn up to 7 days old, 73 children; II. 1 week to 10 years old, 60 children.


GROUP I.
73 CASES
NEWBORN TO 7 DAYS
%
100
90
80
70
60
50
40
30
20
10
0
GROUP 2.
60 CASES
I WEEK TO 10 YEARS
% V9R (-9) V8R (-8) V7R (-7) V6R (-6) V5R (-5) V4R (-4) V3R (-3) VI (-2) VE (1) V2 (2) V3 (3) V4 (4) V5 (5) V6 (6) V7 (7) V8 (8) V9 (9)
PERCENTAGE OF Q-WAVES IN VARIOUS POSITIONS.
PERCENTAGE OF T-WAVES IN VARIOUS POSITIONS WHICH ARE ISOELECTRIC, DIPHASIC OR INVERTED. IT DOES NOT INCLUDE LOW T-WAVES.

Graph 1.

TECHNIQUE

Besides the standard leads (I, II, and III), seventeen precordial leads were recorded as described by Kisch and Richman.[12] The chest lead positions were as follows: V_1, exploring electrode in the mid-sternal line at the level of the fourth intercostal space; V_2, same as V_1, but with the exploring electrode in the left parasternal line; V_3, exploring electrode midway between positions 2 and 4; V_4, exploring electrode in the fifth left intercostal space at the mid-clavicular line; V_5 to V_9, exploring electrode at the same level as V_4 at the left anterior axillary line, midaxillary line, posterior axillary line, and angle of the scapula and left paravertebral line, respectively. The corresponding chest leads on the right side were designated as V-2, V-3, to V-9 or V_1, V_{3R} to V_{9R}, respectively. The midsternal position V_1 was designated as V_E. In Group I (newborn infants) V_2 and V-2 were frequently omitted for technical reasons. In some cases Lead I was taken synchronously with the chest leads as a reference tracing. The Wilson terminal electrode was used, as well as Goldberger's modification of Wilson's

unipolar leads of the left arm (aV_L), right arm (aV_R), and left leg (aV_F). The exploring electrode was the size of a dime and made of silver. A Sanborn Tribeam machine was used.

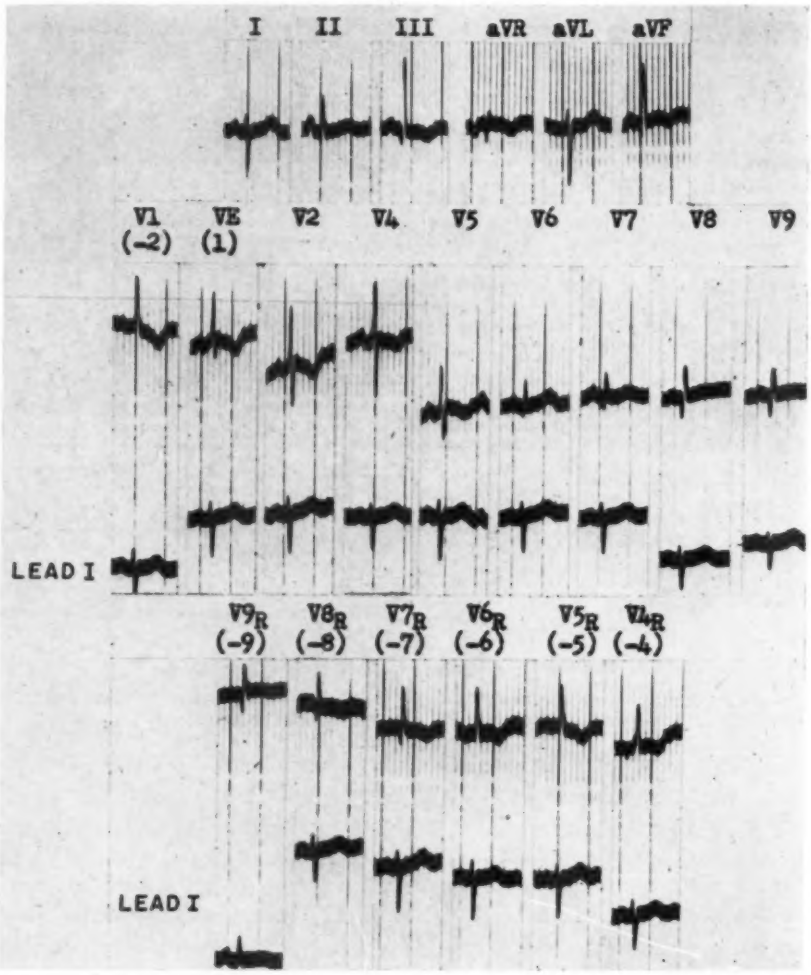


Fig. 1.—Electrocardiogram of M. R., a 3-day-old male infant, showing sinus tachycardia, rate 190, right axis deviation, and a small Q wave in III and aV_F. Chest leads show a Q wave from position V_6 to V_9 and V_{9R} (−9) to V_{7R} (−7). This Q wave when compared with the R wave in Lead I shows it to be synchronous with it. The R wave is greater than the S wave in all the chest leads, i.e., the R/S ratio is greater than 1. T waves are isoelectric, diphasic, or inverted from position V_1 (−2) to V_5, V_8 to V_9, and from V_{9R} (−9) to V_{4R} (−4). Lead I was taken synchronously with the chest leads.

In some of the newborn infants electrocardiograms were taken daily during the first four days of life. In some cases, chest leads were also recorded at the level of the axillary apex. The infants were not restrained in any way; they were kept quiet by offering them a bottle of water.

RESULTS

Group I. Newborn up to 7 Days Old.—The electrocardiographic findings in this group were as follows:

1. The average rate was 140 per minute.
2. There was sinus arrhythmia.
3. Nearly all had right axis deviation or a strong tendency to it. Rarely, an unusual axis deviation was present. A Q wave was occasionally observed in Leads II and III.
4. The P wave was isoelectric, diphasic, or inverted from position V-9 to V-4 (V_{9R} to V_{4R}) and occasionally up to position V_1 and upright in the left chest leads. The P wave was almost invariably inverted in Lead aV_R, occasionally inverted in aV_L, and usually upright in aV_F.

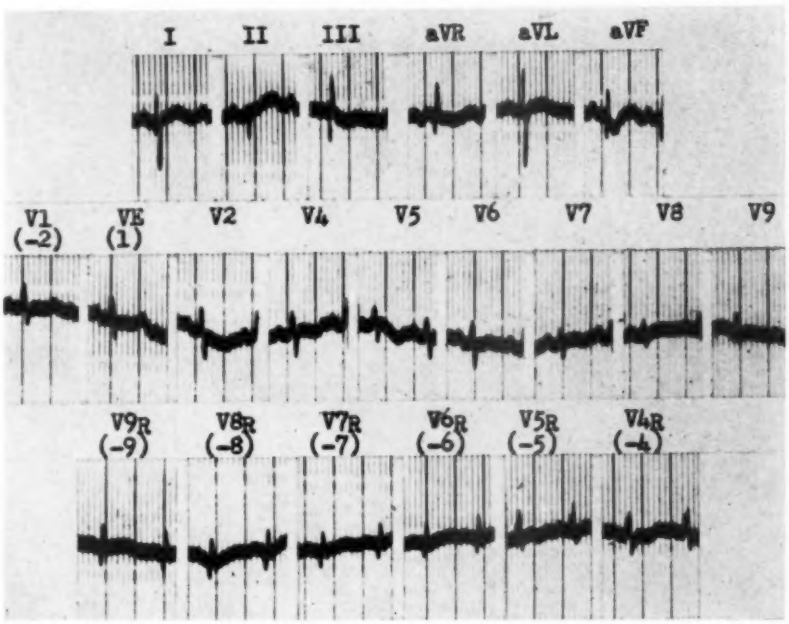


Fig. 2.—Electrocardiogram of F. W., a 3-day-old female infant, showing sinus tachycardia, rate 150, right axis deviation, and a deep Q wave in III and aV_F. Chest leads show a Q wave in V_9 and V_{9R} (− 9), to V_{6R} (− 6). R waves are greater or equal to the S waves in all the chest leads, i.e., R/S ratio is not less than 1 in any position. T waves are isoelectric, low, diphasic, or inverted in all positions except V_5, V_1 (-2), and V_E(1).

5. The Q wave was almost always present from positions V_6 to V_9 on the left side of the chest and V-9 to V-6 (V_{9R} to V_{6R}) on the right side of the chest. The Q wave in the latter was frequently of large size and occasionally as large or even larger than the succeeding R wave. This negative deflection (Q) frequently occurred synchronously with the R wave of the comparing Lead I instead of preceding it, and in some cases the Q wave followed the comparing R wave (Fig. 1).
6. There was a reciprocal relationship between the R and S waves. As the exploring electrode was moved across the precordium from right to left (V-9 to V_9) or (V_{9R} to V_9), a deep Q with a good-sized R wave and no S wave (QR) was present from position V-9 to V-6. In some cases, in position V-6, a small R appeared before the negative deflection (Q) which increased in size up to position V-2 producing an M-shaped complex. In position V_1 these two positive deflections merged into a single positive deflection (R) which increased in size up to position V_5, then decreased in size (Fig. 5). Frequently, instead

of an M-shaped R, it was notched or slurred (Fig. 2). From position V-5 to V-2 only an R wave was frequently present. In position V_1 a small S wave was present which increased in size up to position V_3 or V_4 and, occasionally, up to position V_6, then decreased in size and usually was present in V_7 and even further to the left. The R/S ratio was usually greater than 1 in all these positions, thus differing sharply from the adult electrocardiogram where the ratio is usually less than 1.[12] However, in certain cases a diphasism or equilibrium of R and S was observed. Thus, a left ventricular pattern (qR or R) was observed on the right side of the chest and a right ventricular pattern (RS) on the left side of the chest.

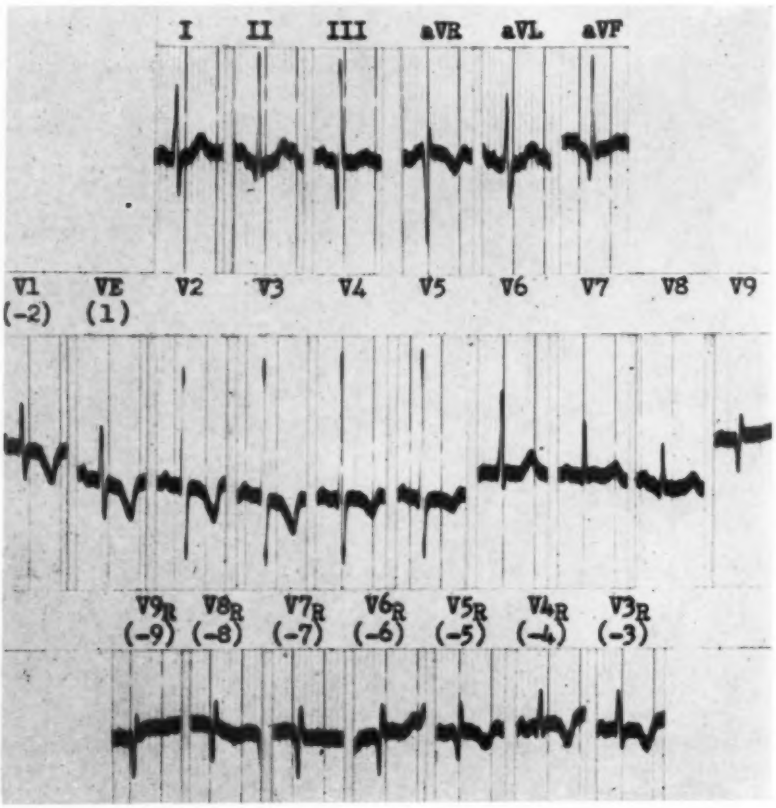


Fig. 3.—Electrocardiogram of C. G., a 4-month-old female infant, showing sinus tachycardia, rate 193, a tendency to right axis deviation, and a deep Q wave in III and aV_F. Chest leads show a deep Q wave in V_9 and in V_{9R} (−9) to V_{5R} (−5). R waves are greater than S waves in all the chest leads, i.e., the R/S ratio is greater than 1 in all positions. T waves are isoelectric, diphasic, or inverted from position V_1 (−2) to V_5 and from V_{9R} (−9) to V_{2R} (−3).

7. T waves were invariably inverted, diphasic, or isoelectric from position V_8 or V_9 on the back of the left chest and V-9 all the way anteriorly to V_1, V_4, and even further to V_5 or V_6.
8. The unipolar extremity leads usually showed a pattern commonly observed in vertical hearts where the axis was shifted toward the right. The aV_L pattern was similar to that obtained from the right precordial lead (RS), and aV_F resembled the left precordial lead (qR), since the left ventricle faced the left leg and the right ventricle faced the left arm. The right arm lead (aV_R) invariably presented inversion of all the complexes. Occasionally, only a QS was present, but usually a QR pattern was obtained.

Daily electrocardiograms, recorded during the first four days of life, showed no change. Electrocardiograms taken at the level of the axillary apex did not show any significant differences from the conventional positions.

Group II. One Week to 10 Years Old.—In this group it was noted that the older the child the more nearly its electrocardiogram approached that of the adult. In Fig. 7 an electrocardiogram almost like that of an adult is observed in a child 10 years of age.

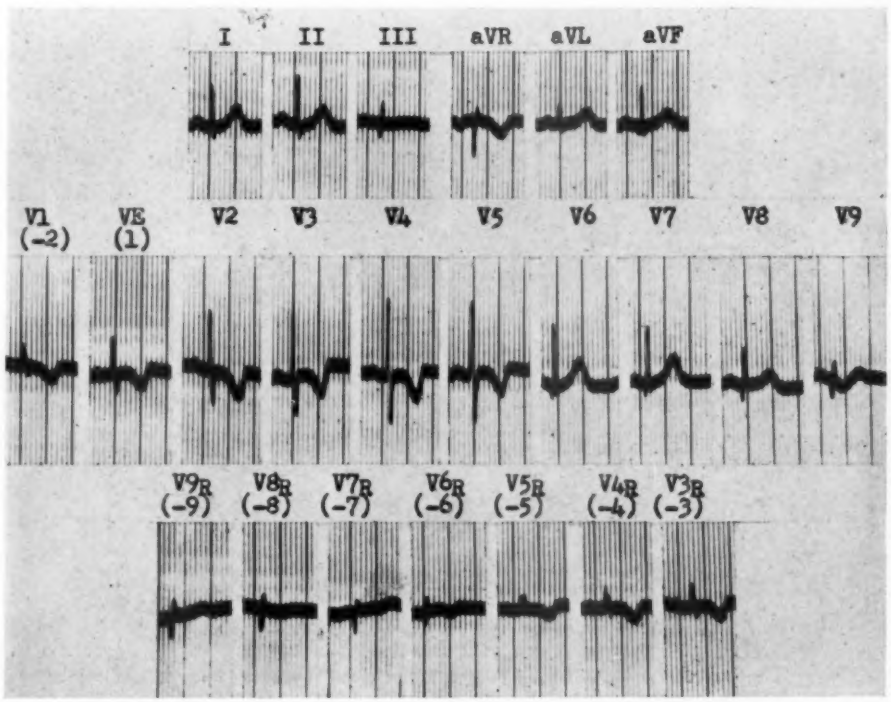


Fig. 4.—Electrocardiogram of R. G., a 2-year-old male infant, showing sinus tachycardia, rate about 120, and no axis deviation. Chest leads show Q waves from V_6 to V_9 and V_{9R} (−9) to V_{6R} (−6). R waves are greater than S waves in all the chest leads, i.e., the R/S ratio is greater than 1 in all positions. T waves are isoelectric, diphasic, or inverted in positions V_1 (−2) to V_5 and V_{9R} (−9) to V_{3R} (−3).

COMMENT

The peculiarities of the infants' electrocardiograms may be due to a variety of morphological characteristics which have been summarized by Battro and Mendy.[9] The chief of these are as follows:

1. In the infant the heart mass is smaller than in the adult, but its ratio to body weight is greater. It is globular in shape.
2. The chest measurements are equal in the anteroposterior, transverse, and vertical dimensions in contrast to the adult thorax in which the anteroposterior diameter is smaller than the transverse.
3. There is greater proximity of the heart to the chest wall and very little or no interposition of lung between the heart and the thoracic wall.

4. There is greater thinness of the chest wall.
5. There is a greater surface of contact between chest wall and right ventricle.
6. The diaphragm is more elevated, and the heart is thus more in a horizontal position.
7. At the beginning of life, size and thickness of the two ventricles are about equal to each other, while at 6 years of age and older, the left ventricular thickness is increased relative to the right.

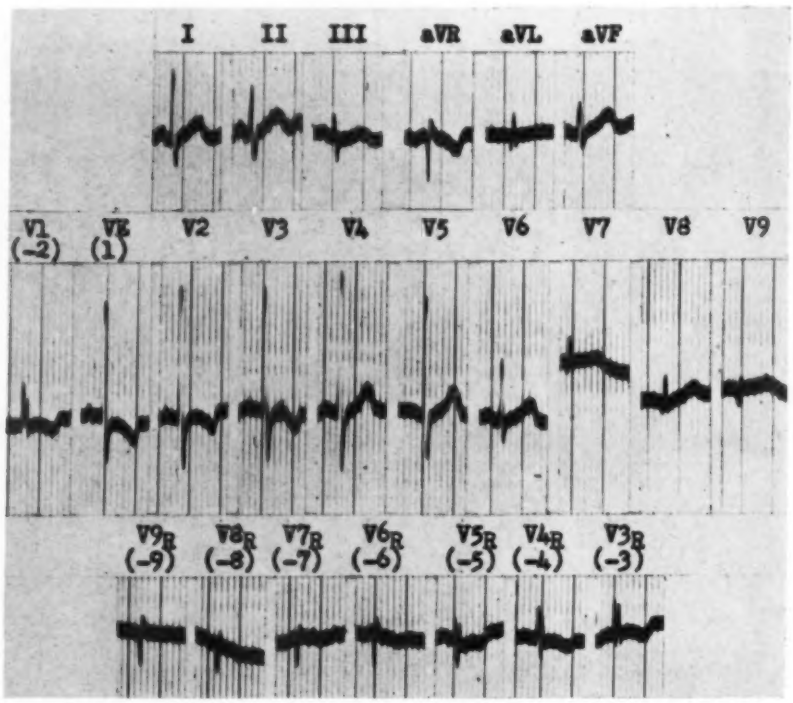


Fig. 5.—Electrocardiogram of F. D., a 4-year-old female child, showing sinus arrhythmia, rate about 150, and unusual axis deviation. Chest leads show a Q wave from V_7 to V_9 and V_{9R} (−9) to V_{7R} (−7). R waves are greater than S waves in position V_{6R} (−4) to V_6, i.e., R/S ratio is greater than 1. Beginning with V_{6R} (−6) to V_1 (−2) the QRS complex is M shaped. T waves are isoelectric, diphasic, or inverted from position V_1 (−2) to V_2 and V_{9R} (−9) to V_{3R} (−3).

The infant heart thus differs from the adult heart in size, shape, and location with respect to the thoracic wall. These differences are carried over to childhood and gradually disappear at various stages of development.

The electrocardiographic configurations at the different stages of infancy to childhood may be explained on the basis of the enumerated factors, especially the different ratio of left and right ventricular muscle masses. The ratio of left to right ventricular muscle mass increases gradually up to the adult stage, thus producing a change in the electrocardiogram from a predominantly right ventricular pattern to a left ventricular pattern.

The normal sinus impulse, after traversing the atrioventricular node and bundle, courses through both bundle branches and the Purkinje system to the myocardial tissue and is activated from this area to the subepicardium. A stimulus spreading toward the location of the exploring electrode (V) will record a

positive deflection (R), and when the stimulus is spreading away from the exploring electrode, it will record a negative deflection (S); also, the greater the relative thickness of the muscle mass the greater the deflection. In the adult the left ventricular wall is relatively much thicker than the right, and a stimulus going toward the exploring electrode in the left chest lead (V_5) will record a positive deflection (R), and the intrinsic deflection will be delayed as compared to V_1. Conversely, when the exploring electrode (V) is placed on the right chest (V_1) at a point where it is facing the relatively thin right ventricular wall, the QRS complex will consist of a small positive deflection (R) followed by a large negative deflection (S), and the intrinsic deflection will occur earlier than in V_5.

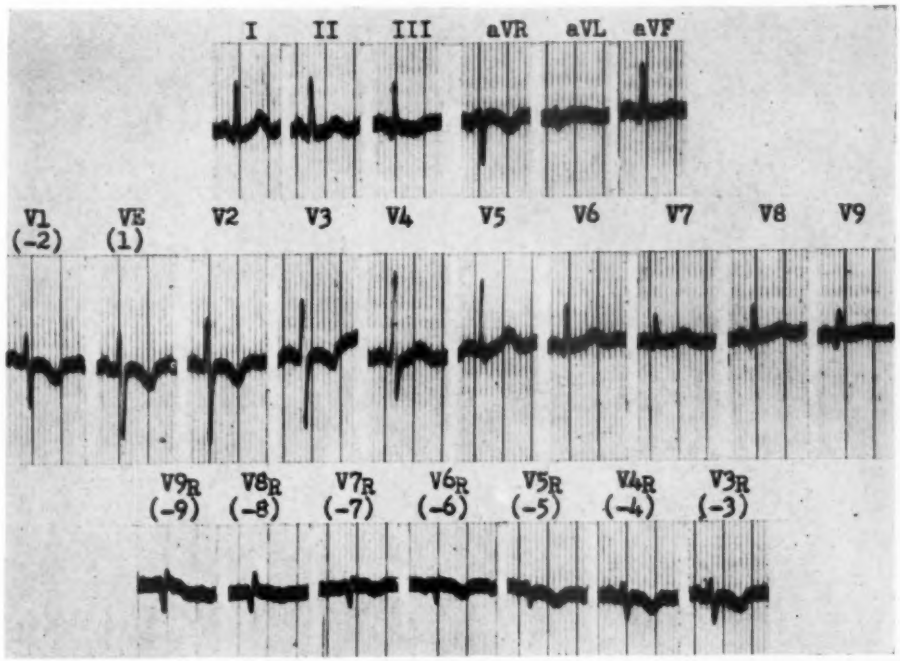


Fig. 6.—Electrocardiogram of R. S., a 6½-year-old male child, showing sinus tachycardia, rate 140, and a tendency to right axis deviation in the unipolar extremity leads. Chest leads show small Q waves in V_6 to V_9 and deep Q waves from V_{9R} (−9) to V_{8R} (−6). R waves are smaller than S waves in position V_1 (−2) to V_2, i.e., R/S ratio is less than 1. T waves are isoelectric, diphasic, or inverted from positions V_1 (−2) to V_2 and V_{9R} (−9) to V_{3R} (−3).

The onset of the intrinsic deflection is the time interval from the beginning of the QRS complex to the peak of the R wave. It is supposed to represent the instant the excitatory process, traveling from the endocardial surface, reaches the epicardial surface of the myocardium underneath the exploring electrode.

In view of recent observations, the interpretation given to the R wave and its intrinsic deflection may be questioned. Intracavity leads obtained from the normal human right ventricle have shown an early left-to-right septal activation which would logically contribute to the formation of the R wave in the right chest leads. Furthermore, these investigators reported simultaneous right precordial leads (V_1) and right intracardiac leads. They found almost identical

small R waves in both instances. They also observed the initial R wave in transient right bundle branch block which remained exactly the same after subsidence of the block. It would then appear logical to conclude that the R waves of intra- and extracardiac origin, as well as the initial R wave in right bundle branch block, are due to septal activation. It was also shown by Wilson and associates, as well as by Sodi-Pallares and his group, that the activation of the subepicardial region occurs during the inscription of the intrinsic deflection.[13-16] The electrical potentials produced by right ventricular activation serve to lessen the amplitude of the S wave in the right chest lead (V_1) and the R wave in the left chest lead (V_5).[17]

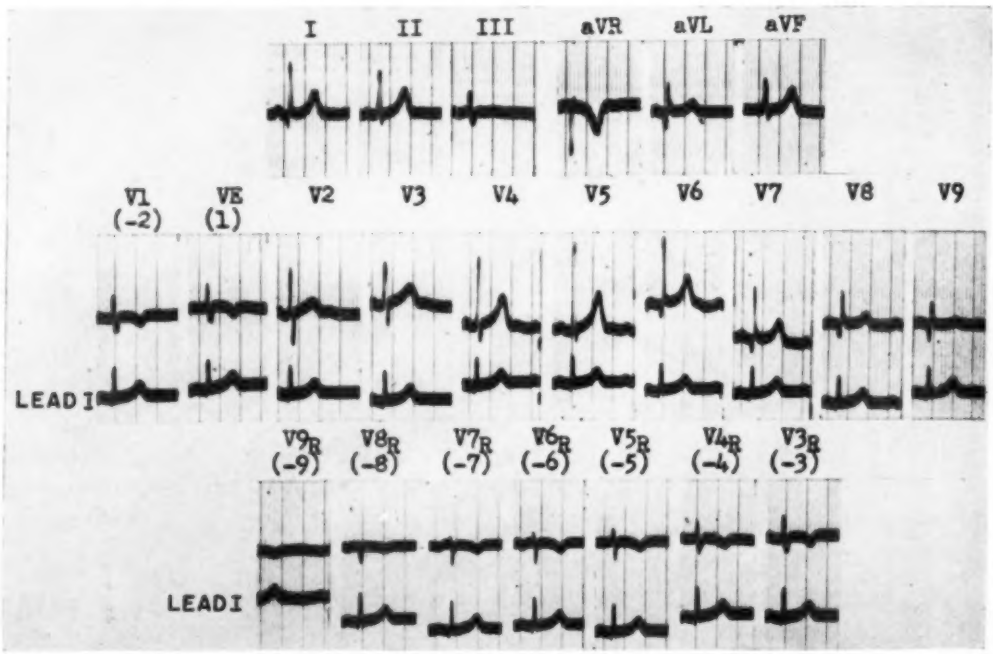


Fig. 7.—Electrocardiogram of L. W., a 10-year-old male child, showing regular sinus rhythm, rate 88, no axis deviation, and a small S wave in III. Chest leads show Q waves from V_6 to V_9 and V_{8R} (−8). Comparing Lead I to other leads shows the Q wave to be synchronous with the R wave except in V_6 where the Q wave precedes the comparing R wave. R waves are smaller than S waves from position V_{7R} (−7) to V_{5R} (−5), i.e., R/S ratio is less than 1. T waves are inverted from V_1 (−2) to V_E (1) and V_{9R} (−9) to V_{3R} (−3). Lead I was taken synchronously with the chest leads.

In a small percentage of patients, an M-shaped R wave was observed in V_1 and/or other right chest leads (Fig. 5). It is thought that the initial R wave is not due to activation of the right ventricular wall but may be due to septal effect, while the secondary R wave may be due to conus arteriosus activation.[18]

In the newborn infant (Group I) there is a relative hypertrophy of the right ventricle as compared with the left. This fact may explain the predominance of the R over the S wave in the right as well as in most of the left chest leads, thus resulting not only in an R/S quotient of 1 or more, but also in a delay of the in-

trinsicoid deflection on the right side of the chest as compared to the left. In Group II, however, the older the child the more predominant is the left ventricle as compared to the right, and, thus, isodiphasism and even predominance of the S over the R deflection may be present in V_1, resulting in an R/S quotient of less than 1, and the intrinsicoid deflection is delayed on the left side of the chest as compared to the right.

The frequency of a qR or R pattern on the right side of the chest and an Rs pattern on the left side of the chest in children may be influenced also by the position of the heart and by rotation on its various axes. This pattern is similar to the one observed in the adult electrocardiogram where right ventricular hypertrophy and a clockwise rotation are present, as in chronic cor pulmonale or mitral stenosis. However, the onset of the intrinsicoid deflection occurs much earlier in a pure positional change as compared to a change due to hypertrophy (usually less than 0.04 second in V_1). It is noted that the younger the child the more the transition point is to the left and vice versa.

The T wave is the wave of ventricular repolarization. The predominantly negative T waves found in the precordial V leads may be explained on the basis of ventricular repolarization which is different from that of the adult. This may be explained by the increased thickness of the right ventricle as compared to the left in children, contrary to what is usually found in the adult. As in the case of the QRS complex the negativity of the T wave may also be due to the position of the heart in the newborn infant. The changes produced by the elevated diaphragm may be analogous to the inversion of the complexes produced by an elevated diaphragm in complete expiration, during the last months of pregnancy, and so forth.

The normal configuration of the augmented unipolar limb leads is influenced by the potential variations of the precordial surface which faces toward each extremity, which, in turn, is dependent upon the anatomical position of the heart. The base of the heart, which faces the right arm, is comparatively fixed in position by the attachments of the great vessels, and thus the pattern of aV_R is generally uniform. However, the apical portion of the ventricles, which face toward the left, is freely movable and may rotate on its various axes and may, therefore, vary greatly in position. Consequently, the left arm pattern (aV_L) and the left foot pattern (aV_F) are normally subject to wide variations.

The right arm lead (aV_R) is derived from the potential variation of the endocardial surface of the verticular cavities, atria, great vessels, and little or none of the epicardial surfaces of either ventricle. This results in inversion of all the complexes. The QRS pattern is subject to variations depending on whether the right arm faces the cavity of the right ventricle, producing an rS complex, the left ventricular cavity, producing a QS complex, or part of the epicardium and cavity, producing a qR complex.

The left arm lead aV_L will resemble V_5 or V_6 if the left ventricle faces the left arm, as in a transverse position (qR), or will resemble V_1 or V_2 if the right ventricle faces the left arm (rS), as in a vertical heart. aV_L may also present the QRS pattern that is observed in the precordial leads in the transition zone (V_3) if the axis is in an intermediate position (RS, RSR).

The left leg lead (aV_F) will resemble V_5, V_1, or V_3 depending on whether the left ventricle, right ventricle, or the intermediate zone is facing the foot, producing qR, rS, and RS complexes, respectively.

In Group I of our cases (infants) the augmented unipolar extremity leads resembled those of a vertical heart pattern, and, as the infant grew older (as in our Group II), the QRS complexes assumed the intermediate zone pattern, and, rarely, a transverse heart pattern was present.

The standard leads I, II, and III usually showed a right axis deviation (Group I) because of the predominance of the right ventricle. As the child grew older (Group II), the right axis deviation disappeared, and, rarely, a left axis developed. The latter changes were probably due to predominance of the left ventricular mass and positional changes.

SUMMARY AND CONCLUSION

1. A study was made of the electrocardiograms of 137 normal infants and children, ranging from newborn infants to children 10 years of age.

2. Standard leads and the unipolar chest and extremity leads with the Goldberger modification were employed.

3. A gradual change was observed from the newborn infant to the child 10 years old, at which period an adult type electrocardiogram was observed.

4. The peculiarities seen at birth and early infancy consisted of right axis deviation in the standard leads, vertical position of the heart in the unipolar extremity leads, and a predominance of R over the S waves in the precordial leads. The R/S quotient was above 1 in all the chest leads in contrast to the adult electrocardiogram in which S predominates over R in V_1 to V_3, producing an R/S quotient of less than 1. As the child grew older, a tendency to diphasism of R and S was observed, and at the age of 10 years, a quotient of less than 1 was observed.

5. The T waves at birth and in early infancy were inverted, diphasic, or isoelectric over the left chest even up to position V_6. By the age of 10 years a positive T wave was recorded in V_4.

6. The possible causes of the differences in the infant and adult electrocardiograms have been discussed. These included variations in size and configuration of the thorax, the ratio of right and left ventricular muscle mass, and the position of the heart.

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ABERRANT VENTRICULAR CONDUCTION

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ABERRATION of a supraventricular impulse[1] giving rise to an altered form of the ventricular complex in the electrocardiogram tends to appear if an impulse occurs early in diastole of the preceding beat before recovery has been completed in all parts of the conducting tissues. Lewis and Master[2] have demonstrated in their experiments on atrioventricular conduction that the recovery curve for a given cycle is influenced by the length of the preceding cycle, and Scherf[3] pointed out that the same factor is responsible for variations of intraventricular conduction. This can be applied to premature systoles of supraventricular origin. Of two premature systoles with identical coupling but with varying duration of the preceding cycle, the one which follows the longer cycle is more prone to exhibit aberrant conduction, since the duration of the refractory period is shorter after a shorter preceding cycle. The purpose of this report is to present clinical examples demonstrating the mechanism of aberrant conduction of supraventricular impulses, to emphasize the influence of cycle length upon refractory period, and to point out the differential diagnosis between ventricular premature systoles and aberrant ventricular conduction in cases of auricular fibrillation or auricular flutter with a varying ratio of atrioventricular conduction.

Auricular Premature Systoles With Fixed Coupling and Aberrant Ventricular Conduction of Those Premature Impulses Which Follow a Long Pre-extrasystolic Cycle.—Fig. 1 shows a record obtained from a 63-year-old patient with hypertensive arteriosclerotic heart disease. Auricular premature systoles from the same focus gave rise to short runs of bigeminal rhythm. Whereas the first premature systole showed only very slight aberration, those of the subsequent couples showed a pattern of right bundle branch system block. The aberration is attributed to the postextrasystolic pause after the first premature systole, which lengthened the pre-extrasystolic cycle of the second premature systole, and to the identical effect of the second premature systole upon the third one.

Atrioventricular Nodal Premature Systoles Occurring in Pairs With Aberrant Ventricular Conduction Only of the First of the Two Premature Systoles.—Fig. 2 shows a record obtained from a 67-year-old patient with arteriosclerotic heart disease. As a result of marked slowing of atrioventricular conduction of the

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second beat of the couple of premature systoles, the R-R distances between the sinus beat and the first premature systole and between the first and second premature systoles became equal. The aberration of the first premature ventricular complex is attributed to the longer pre-extrasystolic cycle.

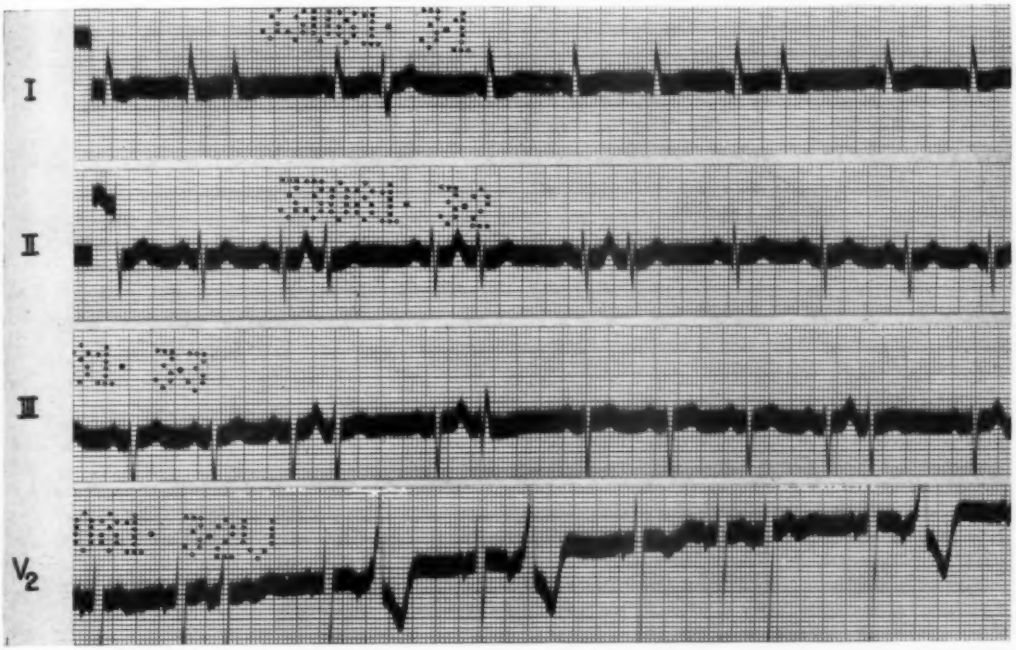

Fig. 1.—Auricular premature systoles with fixed coupling and aberrant ventricular conduction of those premature impulses which follow a long pre-extrasystolic cycle. Discussed in text.

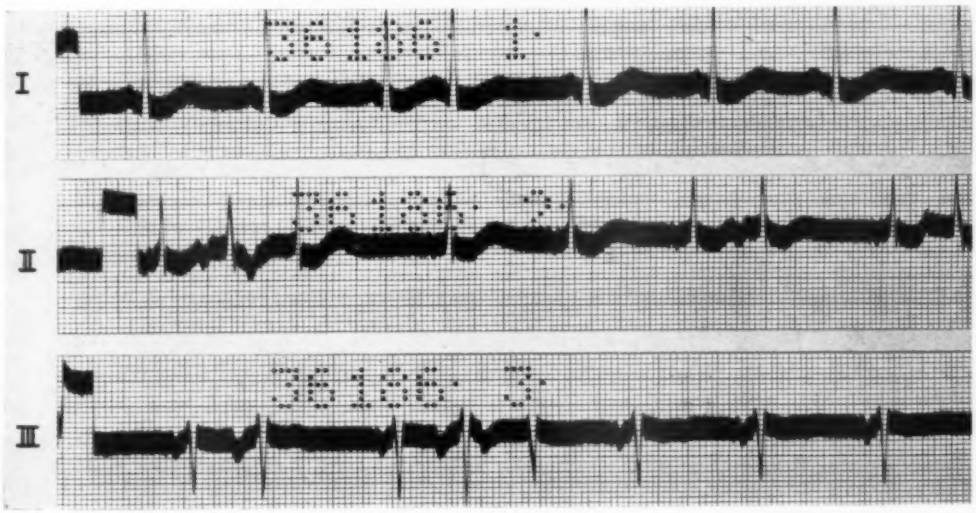

Fig. 2.—Atrioventricular nodal premature systoles occurring in pairs with aberrant ventricular conduction only of the first beat of the pair which follows the longer pre-extrasystolic cycle. Discussed in text.

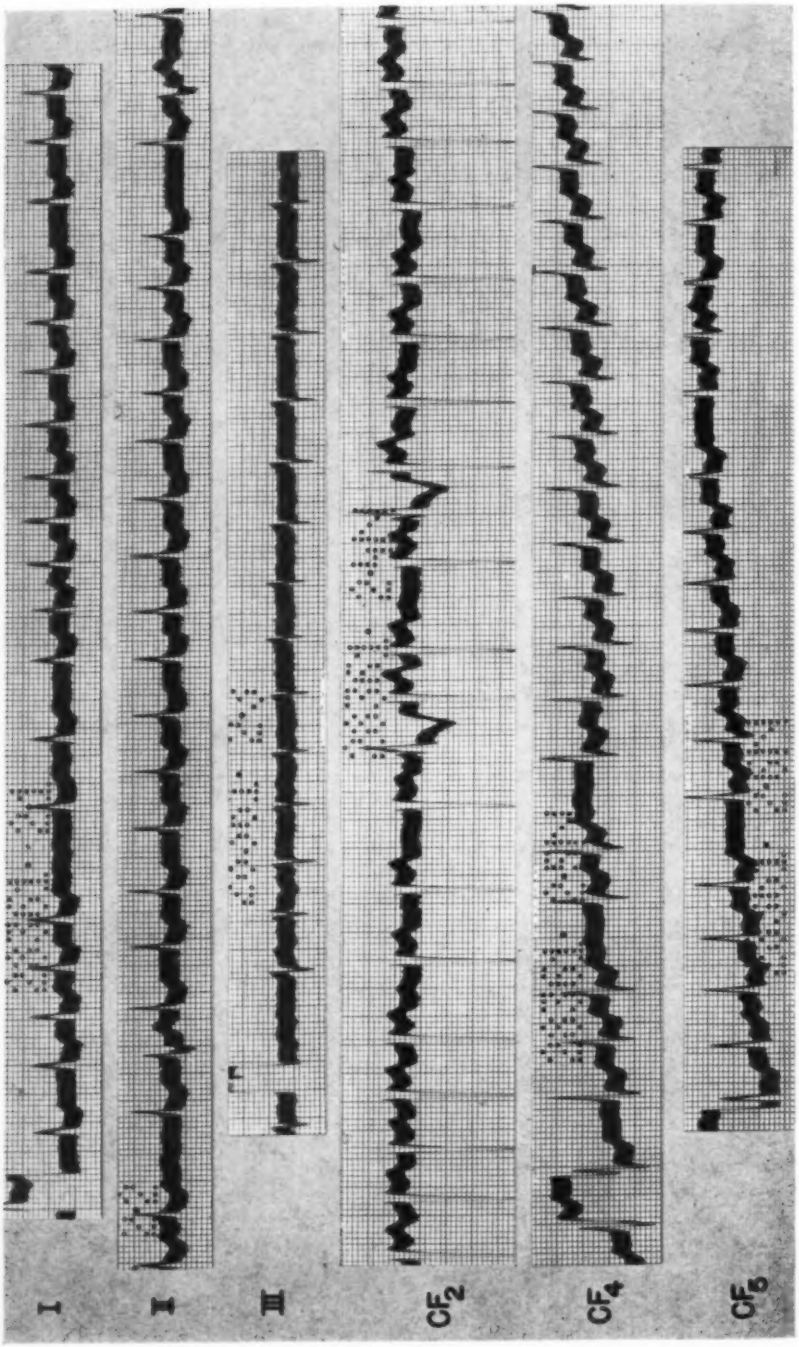

Fig. 3.—Auricular fibrillation with a rapid ventricular rate and aberrant ventricular conduction of those beats which terminate a short cycle which follows upon a long cycle. Discussed in text.

Auricular Fibrillation With a Rapid Ventricular Rate and Aberrant Ventricular Conduction of Those Beats Which Terminate a Short Cycle Which follows Upon a Long Cycle.—Fig. 3 was obtained from a 69-year-old patient with arteriosclerotic heart disease. Whenever a short cycle, measuring 0.40 second or less, followed upon a long cycle, measuring 0.58 second or more, the short cycle was terminated by a ventricular complex showing right bundle branch system block. The coupling of the aberrant beats varied, and with one exception (in Lead CF_4) they were not followed by a "compensatory pause."

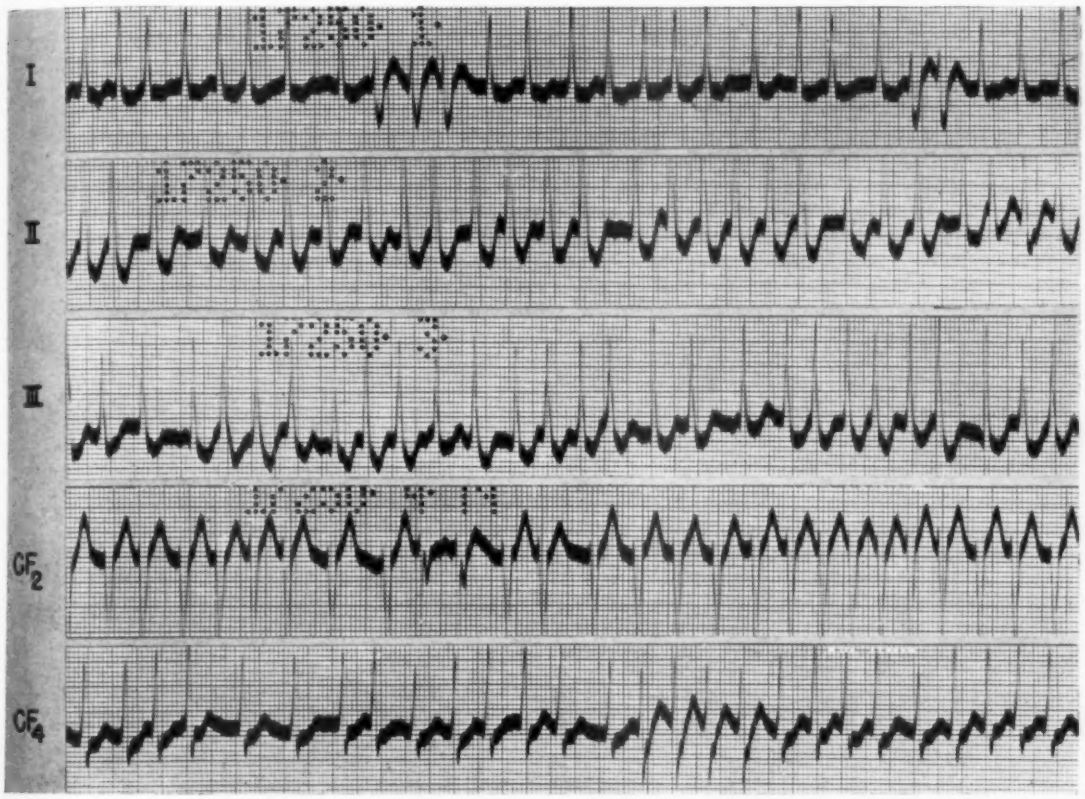

Fig. 4.—Auricular fibrillation with a rapid ventricular rate and runs of beats with aberrant ventricular complexes initiated by an aberrant beat which terminates a short cycle which follows upon a long cycle. Discussed in text.

Auricular Fibrillation With a Rapid Ventricular Rate and Runs of Beats With Aberrant Ventricular Complexes With the First Aberrant Beat Terminating a Short Cycle Which Follows Upon a Long Cycle.—Fig. 4 shows a record obtained from a 54-year-old patient with hypertensive heart disease before digitalization. With few exceptions the initial aberration occurred if a cycle measuring 0.28 second or less followed upon a cycle measuring 0.40 second or more. Again the coupling of the first aberrant complexes varied, and there was no "compensatory pause" after the last aberrant complexes.

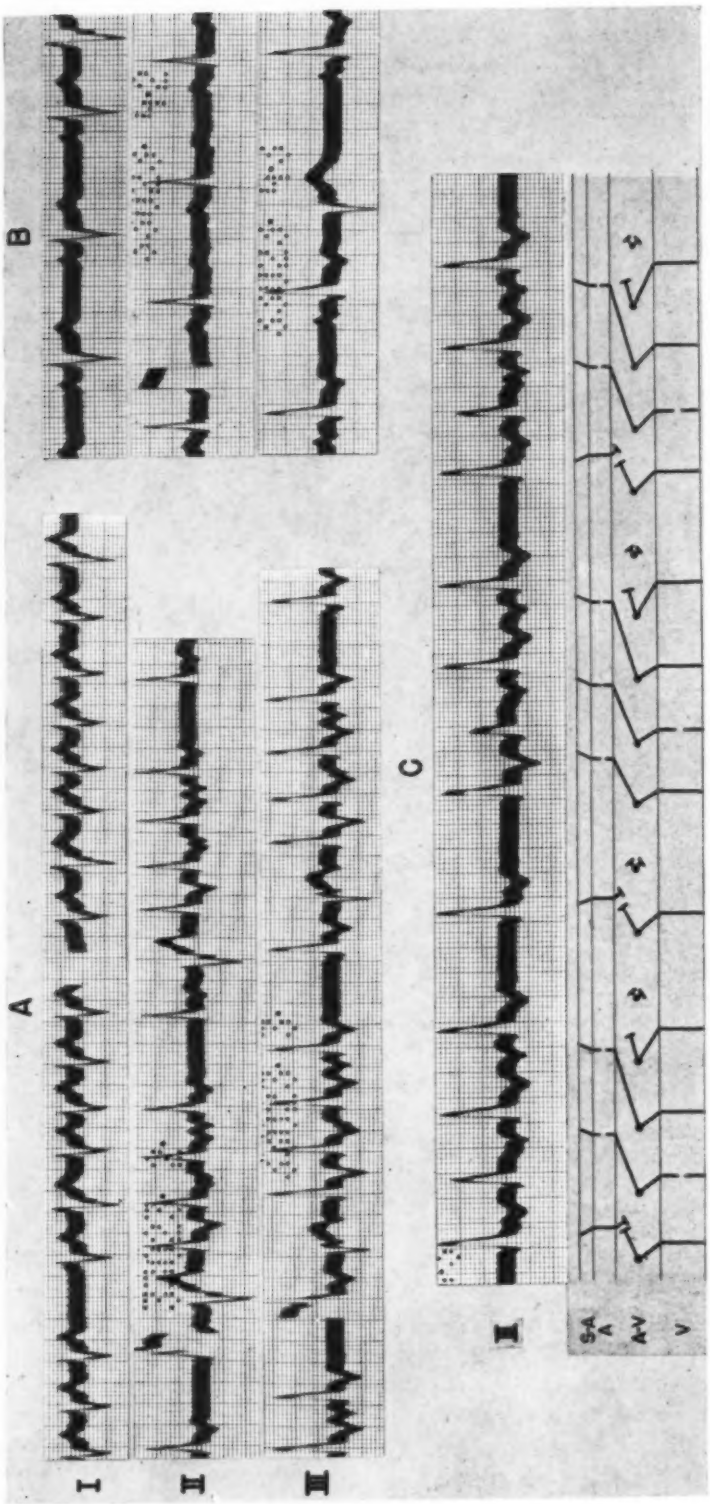

Fig. 5.—Atrioventricular nodal paroxysmal tachycardia with retrograde conduction and irregular auricular and ventricular rates due to second-degree block affecting both atrioventricular and ventriculoauricular conduction. Aberrant ventricular conduction of the second impulse occurs after the intermission. Discussed in text.

Supraventricular Paroxysmal Tachycardia With Dropped Beats and Aberrant Conduction of the Second Beat After the Intermission.—Fig. 5 shows a record obtained from a 72-year-old patient with arteriosclerotic heart disease (*A*) before therapy, (*C*) after quinidine (four days after *A*), and (*B*) after digitalization (seven days after *C*). Records *A* and *C* show an atrioventricular nodal tachycardia with retrograde conduction. The irregularity of the auricular and ventricular rates was due to conduction disturbances which are indicated in the diagram below record *C*. The supraventricular origin of the tachycardia is confirmed by the record with sinus rhythm (*B*) showing the same pattern of right bundle branch system block. The aberration of the complexes terminating the short cycles following the intermissions in record *A* and, less marked, in record *C* with the slower atrioventricular nodal rate is explained by the effect of the long preceding cycle upon the refractory period of the right bundle branch system. A similar aberration is seen in the last beat of a long run of conducted beats in Lead I of record *A* and in the premature beats recorded in *B* after restoration of sinus rhythm.

COMMENT

The distinction between ventricular premature systoles and supraventricular beats with aberrant ventricular conduction is simple if the premature ventricular complexes are preceded by premature P waves. However, it becomes difficult (a) when P waves with a retrograde contour follow the ventricular complexes, (b) when no P waves can be identified, and (c) when auricular fibrillation or auricular flutter is present. Where such aberrant ventricular complexes occur in runs they may be mistaken for ventricular paroxysmal tachycardia[4] and the patient may be deprived of the benefit of digitalization. In Figs. 1, 2, 3, and 5 the aberration of single beats demonstrates how the recovery curve for a given cycle is influenced by the length of the preceding cycle. Gouaux and Ashman[5] have pointed out how the same mechanism may initiate a run of aberrations in cases of auricular fibrillation and simulate ventricular paroxysmal tachycardia (Fig. 4). The initial aberration indicates delayed activation of one ventricle via the intraventricular septum. The same aberration is seen in the subsequent beat if the delay in the activation of this ventricle was such as to cause refractoriness of its main bundle branch at the time of the arrival of the next supraventricular impulse. The aberration is maintained in the following beats until a supraventricular impulse occurs late enough in the cycle to permit recovery of both bundle branches. Actually, the same mechanism may account for a ventricular contour of any supraventricular tachycardia. This is undoubtedly facilitated in the presence of a latent intraventricular conduction defect and should be suspected whenever a right bundle branch system block pattern presents itself. The latter was stated[5] to be found in 85 per cent of all patients whose electrocardiograms revealed aberration in the distribution through the ventricles of premature supraventricular impulses.

In the presence of auricular fibrillation it is difficult to distinguish between ventricular premature systoles and aberration of supraventricular impulses because ventricular premature systoles also have a tendency to occur after a beat

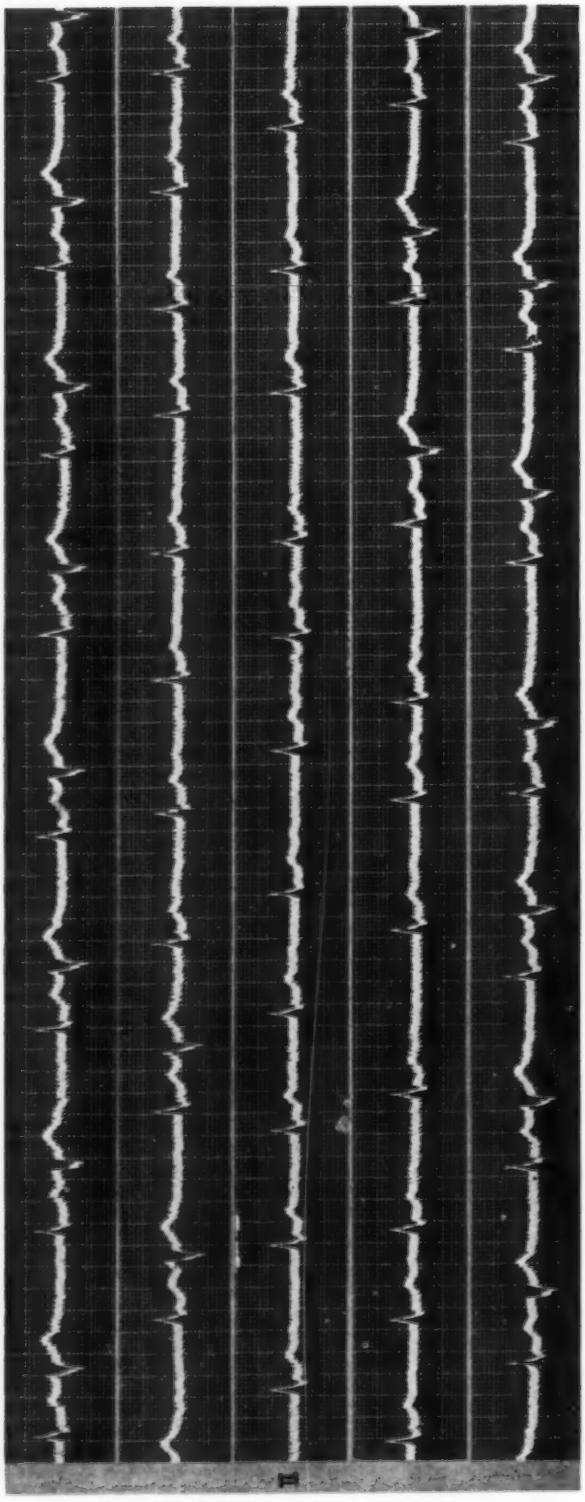

Fig. 6.—Auricular fibrillation with slow ventricular rate and intermittent bigeminal rhythm due to ventricular premature systoles of similar contour and almost fixed coupling. Discussed in text.

which terminates a long cycle ("bigeminy rule" of Winternitz[6]). Such an instance is shown in the record of Fig. 6 obtained from a 63-year-old patient with mitral stenosis after full digitalization. Here, bigeminal rhythm due to ventricular premature systoles of similar contour and almost fixed coupling was terminated when the postextrasystolic interval shortened (second row) and was resumed when it lengthened (fourth row). A single long cycle tended to usher in a long run of bigeminal rhythm because of the tendency to retrograde conduction into the atrioventricular junction of the ventricular ectopic impulses giving rise to a "compensatory pause." As a rule, such a pause is missing after aberrant conduction of supraventricular impulses (Figs. 3 and 4). The lack of a "postextrasystolic" pause, together with variations in the coupling of the aberrant beats, can be used as a guide, but should not be considered infallible criteria, in the differential diagnosis between aberration and ventricular premature systoles in the presence of auricular fibrillation or flutter.

SUMMARY

1. Examples are presented of aberrant ventricular conduction of supraventricular impulses dependent upon the duration of the preceding ventricular cycle.

2. The criteria for the differential diagnosis of ventricular premature systoles and aberrant ventricular conduction in cases of auricular fibrillation and auricular flutter with irregular ventricular rate are pointed out.

3. The clinical importance of the recognition of aberrant ventricular conduction, particularly in the differential diagnosis of paroxysmal tachycardia, is pointed out.

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RHEUMATIC HEART DISEASE WITH NORMAL RHYTHM AND VERY LARGE "a" WAVES IN THE JUGULAR PULSE

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LARGE vascular pulsations in the neck can be of arterial or venous origin. Slight pressure over the jugular bulb obliterates the second and not the first. Exaggerated venous pulsations have been shown to be due to (a) tricuspid regurgitation and stenosis or (b) summation of "a" and "c" waves of the venous pulse in cases of nodal rhythm or, inconstantly, incomplete auriculoventricular block. Both of these mechanisms cause large systolic ventricular pulsations.

We have observed recently two patients who showed a very large venous pulsation in the neck due to a different mechanism. The unusual character of these pulsations and some possible considerations of the dynamics of tricuspid disease stimulated us to report these observations.

CASE REPORTS

CASE 1.—P. A. was first seen in the clinic in 1947, when he was 15 years old, for breathlessness and pulmonary edema. He had had a severe attack of rheumatic fever at 12 years of age. Upon examination he appeared in good general condition with slight cyanosis and no edema. There were no pulsations in the neck with the patient either in the standing or in the sitting position; in the lying position the jugular pulsation was normal. There was at the cardiac apex a diastolic and presystolic rumble with a thrill and a loud first sound. The second pulmonary sound was reduplicated and loud. The radial pulse was regular and small; the arterial pressure measured 100 mm. Hg systolic and 60 mm. Hg diastolic. On x-ray examination (Fig. 1,*A*) the heart was found to be a little enlarged and altered in shape; the hilar and lung vessel shadows were much engorged. The electrocardiogram (Fig. 2,*A*) showed right ventricular preponderance with large, notched P waves.

The patient was seen again in 1950. In the meantime, he had been in fairly good health, under restricted activity. The breathlessness on exertion was slightly increased, but he had had no more pulmonary edema. Over the past year he had felt and seen a strong pulsation in the neck. Upon examination his general condition was found to be still good. The cyanosis was slightly increased. There was no edema. With the patient in the standing position, above both clavicles at the base of the neck, on both sides but more marked on the right than on the left, there was evident a very strong pulsation which gave the impression of an arterial pulsation, as in aortic incompetence. This was abolished, however, by slight pressure of the finger. The pulsation was evident above the clavicle to the extent of 1 cm. in every position—standing, sitting, or lying. With the patient in the recumbent position only, higher in the neck, there appeared a very slight pulsation of apparently normal character. At the apex of the heart the diastolic-presystolic rumble was now accompanied by a slight systolic murmur, with maximal intensity at the xyphoid cartilage. Here the systolic murmur was reinforced during deep inspiration. The liver edge was felt one fingerbreadth below the costal margin; no pulsation was made out. The radial pulse was regular and small. The blood pressure was 80 mm. Hg systolic and 70 mm. Hg diastolic.

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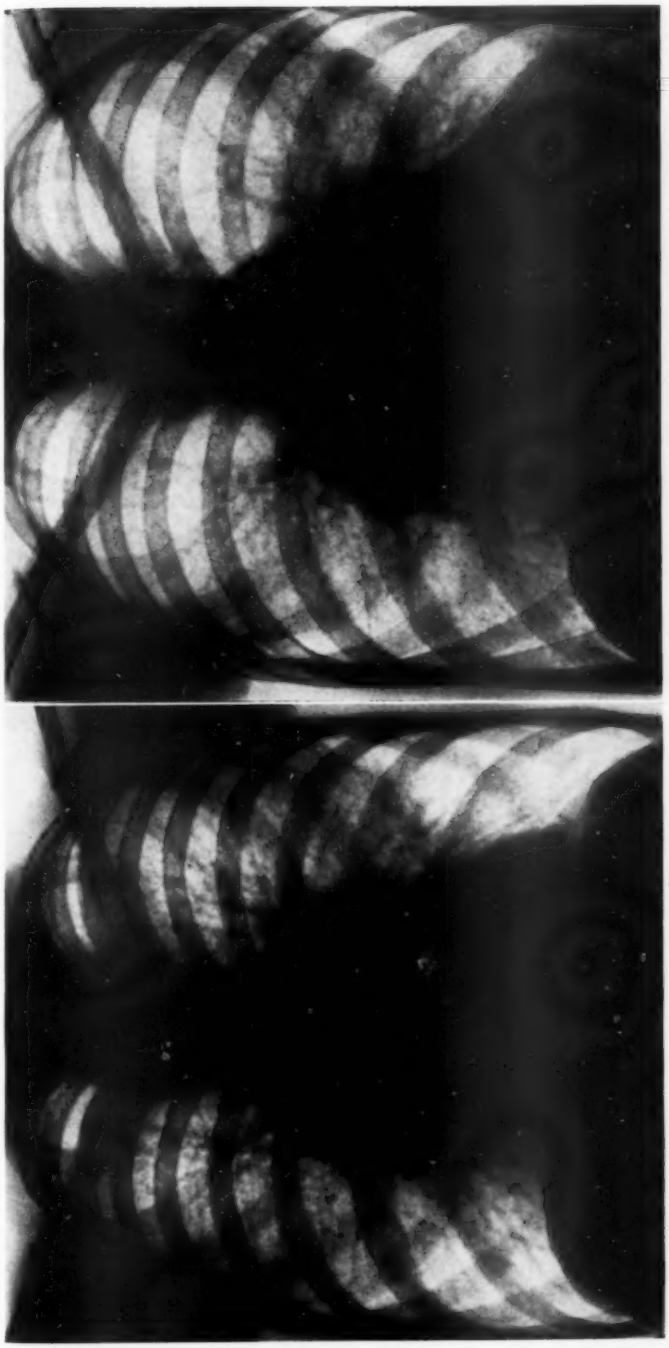
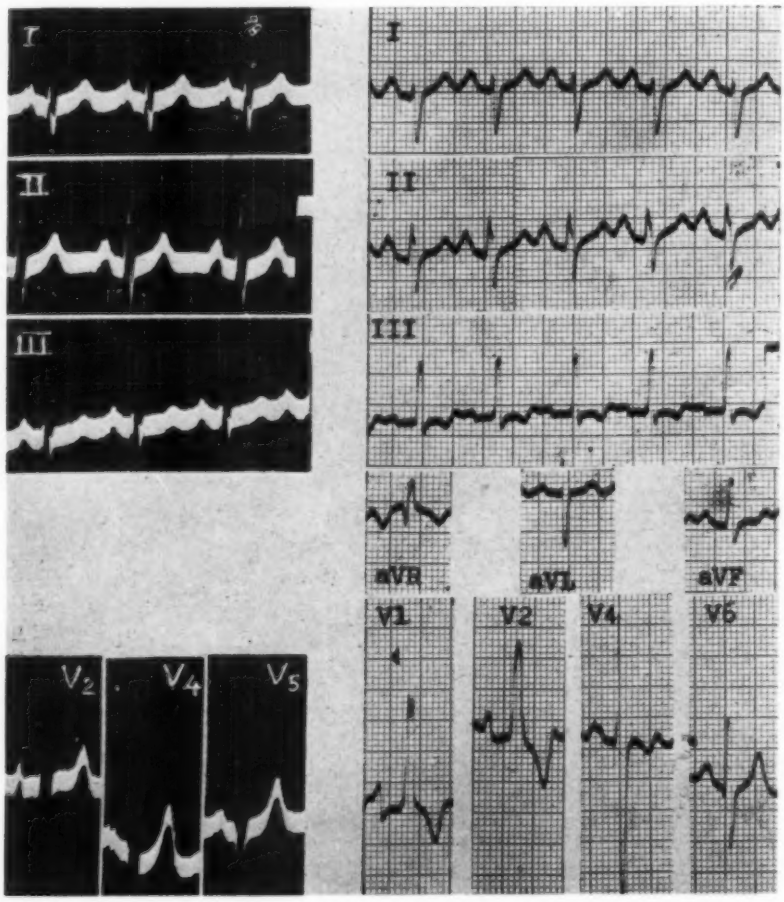


A. B.

Fig. 1 (Case 1).—X-ray films of thoraxes showing change in heart size during a two and one-half year interval. Note the prominence of the right inferior border in the later film.

On x-ray examination (Fig. 1,*B*) the heart was found to be enlarged, especially at the right inferior border, which was also deeply pulsating. The hilar shadows were congested. The electrocardiogram (Fig. 2,*B*) now showed a more marked right ventricular preponderance with intraventricular conduction disturbance (QRS equal to 0.10 second), large P waves, and diphasic T waves with a large intrinsic deflection in V_1. The venous pressure in the arm was 5 cm. of H_2O. The sedimentation rate was normal.



A. B.

Fig. 2 (Case 1).—Electrocardiograms taken at intervals of two and one-half years. Note the right axis deviation and the characteristic P waves in V_1 in the later electrocardiogram.

CASE 2.—L. G., a woman 25 years old, was seen in November, 1949, because of palpitation, slight dyspnea on exertion, slight chest pain, and a strong pulsation in the neck. She had had chorea at 11 years of age, when a "heart murmur" had been diagnosed. At the age of 17 years she had had severe rheumatic fever of seven months' duration, which had terminated following tonsillectomy and the removal of infected teeth. The patient had been in good health thereafter with normal exercise tolerance. Married at 20 years, she had had two children without trouble. For the past year she had observed the appearance of a very definite pulsation in the right supraclavicular region. Her exercise tolerance was still good except for very slight breathlessness and palpitation. She could have continued a completely normal life, but she was concerned about the pulsation in the neck.

Examination disclosed that her general condition was normal without cyanosis or edema. In the supraclavicular region on both sides there was a marked pulsation of arterial appearance, limited to 1 or 2 cm. above the clavicles. The pulsation was very apparent in all body positions; in recumbency there appeared a very slight pulsation of normal character higher in the neck. Compression with the finger easily abolished the pseudoarterial pulsation. At the apex of the heart there were a diastolic-presystolic rumble and a slight systolic murmur. A more intense systolic murmur was heard in the fourth intercostal space at the left sternal border. There was a slight diastolic murmur over the aortic valve area. The first sound was loud at the apex, the second sound loud at the pulmonic area. The radial pulse was 100 in rate, regular, and small. The liver edge was felt one fingerbreadth below the costal border; it was not pulsating. The blood pressure measured 120 mm. Hg systolic and 80 mm. Hg diastolic. A sedimentation rate (Westergren) was 5. On x-ray examination (Fig. 3) the heart appeared to be moderately enlarged, especially at the right inferior border which was deeply pulsating. An electrocardiogram (Fig. 4) showed a vertical axis, large P waves, and diphasic T waves in V_1 with rapid intrinsicoid deflection.

Fig. 3 (Case 2).—X-ray film taken July 15, 1948, before the patient noticed the appearance of the pulsation in the neck. At the time of our examination, the fluoroscopy showed a more enlarged heart, especially at the right inferior border. At this time we were not able to get a radiograph.

PHLEBOGRAPHIC STUDY

By means of a Sanborn Stethocardiette the pulse tracings were made of both patients in the lying position at different levels from the inferior to the upper part of the jugular area.

At the lower part of the neck, just over the jugular bulb, and on the site of maximal pulsation, the tracings were similar in both patients. A wave of short duration but of great amplitude and coincident with the auricular contraction (Figs. 5,*B* and 6,*B*) was evident in both. We would emphasize the fact that the tracings made in this position were recorded with the lowest sensitivity of the machine, because with normal sensitivity it was impossible to record the full

extent of the complexes. We may say that in this position an isolated "a" wave of tremendous amplitude constituted the entire tracing, the other waves being obscured, probably because of the low amplification.

In the tracings made in a higher position (Figs. 5,*C* and 6,*C*), the pulsations were smaller and the sensitivity could accordingly be returned to normal. The "a" wave was here obscured in a plateau, and there was a collapse which was telesystolic-protodiastolic in the first patient and mid-systolic in the second one. In a still higher position (Figs. 5,*D* and 6,*D*), the pulse was quite atypical, but there was no high, isolated "a" wave nor systolic plateau (no incompetence wave).

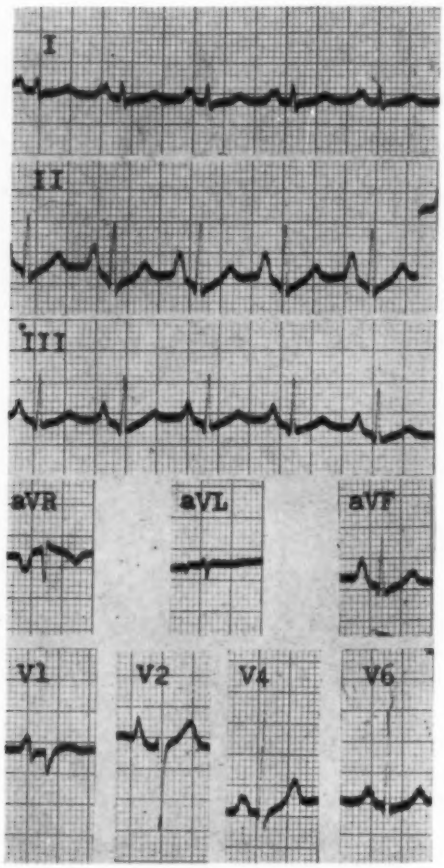


Fig. 4.—Electrocardiogram of Case 2.

COMMENT

1. Mechanism of the Pulsation.—Both patients had chronic rheumatic carditis with mitral involvement; recently, they had both observed the appearance of a large pulsation in the neck. In the first patient, in whom two radiologic examinations were available, one before and one after the appearance of the

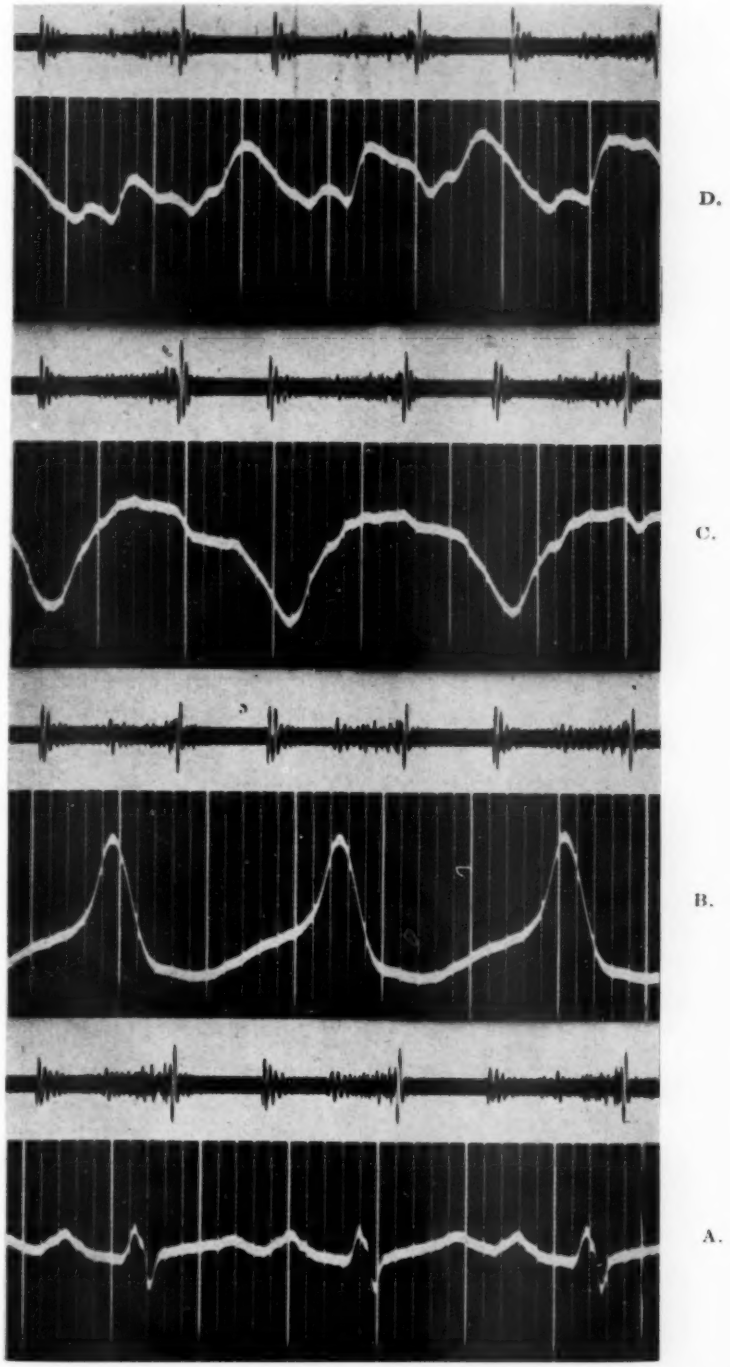


Fig. 5 (Case 1).—(Note *A* at bottom and then proceed upward.) *A*, Electrocardiogram and phonocardiogram at the apex. *B*, Phlebocardiogram at the base of the neck and phonocardiogram. Note the very large "a" wave corresponding to the presystolic murmur and constituting the only wave of the tracing. This tracing was made with low sensitivity of the machine. *C*, Phonocardiogram and phlebogram taken higher in the neck. *D*, Phonocardiogram and phlebogram taken still higher in the neck. Note in *C* and *D* the change in form of the phlebogram and the disappearance of the very large, isolated "a" wave. Both tracings *C* and *D* were made with increased sensitivity of the machine.

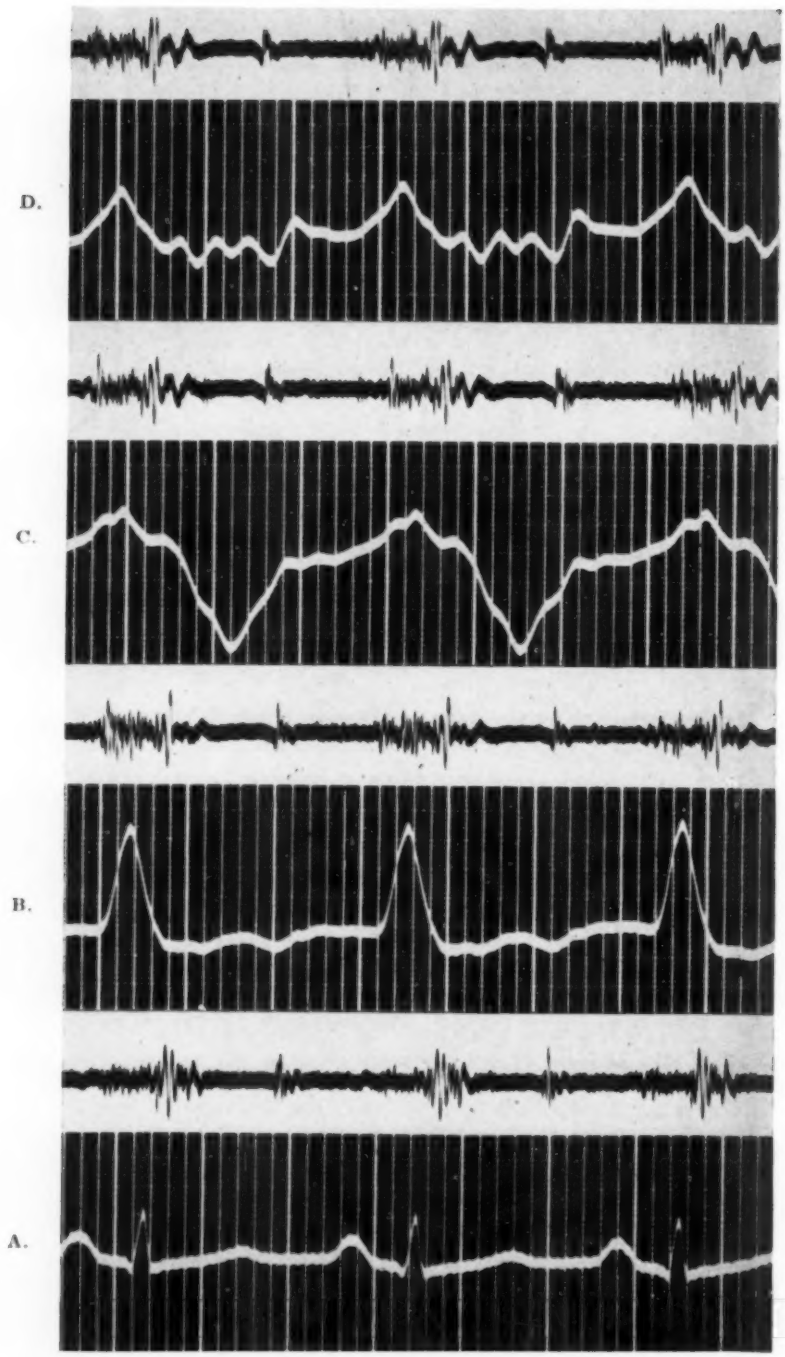


Fig. 6 (Case 2).—Produced in the same way as Fig. 5. The aspects demonstrated by this figure are practically the same as in Case 1.

anomalous pulse, it was demonstrated that the heart had become enlarged in the interim, especially at the right inferior border (Fig. 1). Both patients had, in addition, a systolic murmur over the heart, and the first patient presented the reinforcement of this murmur during deep inspiration, as described by Rivero Carvallo[1] in tricuspid valve disease. The electrocardiogram showed in both cases a right ventricular preponderance or right axis deviation with P waves characteristic of right or of combined auricular enlargement.

It would seem proper to interpret the big "a" wave as due to forceful systole of the right auricle against a tricuspid stenosis.

The fact that a large "a" wave may be found in tricuspid stenosis has been mentioned in the literature, especially by the older authors;[2] in general, however, more attention has been paid to the "incompetence wave" of tricuspid insufficiency.

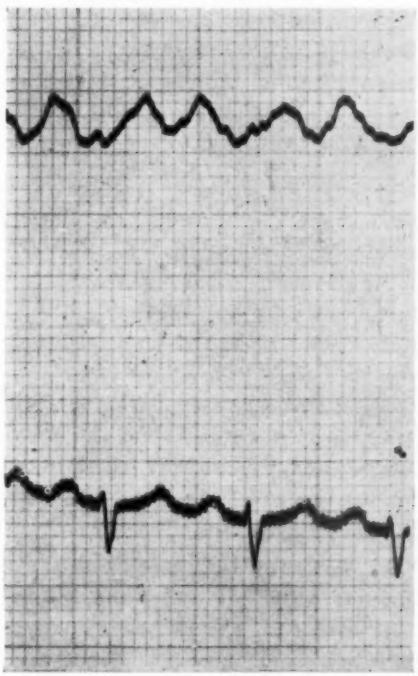


Fig. 7 (Case 1).—Upper tracing: electrokymogram of the right inferior border of the heart. Lower tracing: electrocardiogram of Lead I.

A peculiar and interesting phenomenon in both cases is the observation that the large pulsation was evident only in the jugular bulb and not in the higher vessels. This was probably due to the fact that, in the absence of passive venous congestion, the veins were not dilated and the valves were competent. The valves are situated at the outflow of the internal jugular and subclavian veins in the jugular bulb and, if competent, can arrest any backflow of blood from the right auricle. This is a further demonstration of the fact that the systolic incompetence wave seen in the jugular pulse in cases of tricuspid incompetence is present in the superior veins of the neck, and sometimes in the brachial veins, only if the veins are dilated by chronic venous hypertension and the valves are incompetent.

As a matter of fact, every patient with tricuspid incompetence and distended and pulsating veins has an elevated venous pressure.[3,4] In the only one of our patients in whom the venous pressure was measured, this was found to be normal (5 cm. of H_2O). It is more difficult to understand why the liver was not pulsating in both patients, because as a rule the suprahepatic veins have no valves.[5]

Judged by the character of the jugular pulse, in our patients the stenosis was dynamically pure; no regurgitation wave was demonstrable in the tracings. In one of our patients we were able to take an electrokymogram of the right heart border (Fig. 7) which demonstrated no systolic plateau such as Luisada and Fleischner[6] have seen in left auricular tracings in cases of mitral insufficiency.

It is hard to explain why in both patients there was a systolic murmur over the heart and why in the first instance the murmur had the peculiar character described in tricuspid disease. Probably there was an incompetence, but of so little degree as to be dynamically insignificant.

2. Clinical Significance.—As suggested by Cooke and White,[3] an unusually large pulsation of the internal jugular veins which is present for months and years without significant congestive heart failure is a strong presumptive sign of tricuspid involvement. Cooke and White, like other authors, considered this pulsation to be systolic and due to tricuspid regurgitation. Our cases demonstrate that the pulsation may also be presystolic, as was noted by former observers. Obviously, the pulsation may be presystolic only if a normal rhythm is present, and with tricuspid (and mitral) stenosis this is a rare, and generally an initial, occurrence.

Furthermore, in the current cases described by Cooke and White,[3] by Smith and Levine,[4] and by others, the patients had engorged veins and high venous pressure. In our patients the pulsation was limited to the presystolic part of the venous pulse, the veins were not engorged, and the venous pressure was normal in the patient in whom it was taken, and probably normal in the other patient, too, considering the normal aspect of the veins. We believe that it is possible to state that a systolic pulsation with venous engorgement is presumptive of tricuspid involvement with incompetence, and that a presystolic pulsation without venous engorgement is a presumptive sign of dynamically pure tricuspid stenosis.

The single condition which can give the same type of pulsation without tricuspid stenosis would be a ball thrombus of the right auricle, which is extremely rare. We were able to find in the literature one case of this condition with autopsy report. The phlebographic tracing showed an extremely high "a" wave.[7]

3. Comments on the Natural History of Tricuspid Valvular Disease.—The clinical diagnosis of tricuspid involvement is not easy, but we may make this diagnosis when we see a patient with rheumatic mitral disease in whom the following signs and symptoms are evident and form a peculiar pattern: (a) a long history of cardiac illness; (b) very little dyspnea coexisting with chronic edema of the legs and with a grossly enlarged liver (not always pulsating); (c) relatively good functional capacity; (d) slight pulmonary engorgement; (e) a large heart with clear lungs; (f) a peculiar color of the skin, the combination of cyanosis and slight jaundice. These are all signs and symptoms of chronic congestion of the peripheral venous circulation with liver involvement and with slight congestion of the pulmonary bed.

Our patients presented a very different pattern and demonstrate that on rare occasions the tricuspid involvement may be more precocious and assume a very different hemodynamic character. Here the only signs are local and due to the stenosis without peripheral involvement.

SUMMARY

In two patients with chronic rheumatic carditis with mitral stenosis (and in one patient with aortic regurgitation) there were large venous pulsations limited to the base of the neck. These pulsations consisted of very large "a" waves in the phlebogram.

It is probable that these pulsations were due to tricuspid stenosis without failure and without dynamically active tricuspid incompetence.

I wish to express my appreciation to Dr. Paul D. White of Boston for his kind consideration and revision of this text.

ADDENDUM

Since this paper was submitted for publication, the author has found two additional articles related to the same subject.

Vesell (Vesell, H.: Tricuspid Stenosis—A Simple Diagnostic Sign, Am. J. Med. **7**:497, 1949) describes a case of mitral, aortic, and tricuspid valvular disease with necropsy findings. The patient showed marked presystolic pulsations in the neck. There were signs of severe cardiac failure with engorged veins, and the venous pressure was 17 cm. of water. No phlebographic tracings were taken. Dr. Vesell proposed a simple maneuver for the timing of the impulse, the contemporary palpation with two fingers of the jugular vein and of the episternal notch. In a personal communication to the author, Dr. Vesell wrote that in a subsequent similar case he was able to record sphygmographic and electrokymographic tracings which confirmed his statement. He further pointed out the usefulness of the sign for the bedside diagnosis of tricuspid stenosis.

Grishman and associates (Grishman, A., Kroop, I. G., Steinberg, M. F., and Dack, S.: Presystolic Pulsations of the Liver in the Absence of Tricuspid Disease, Am. Heart J. **40**:731, 1950) studied fourteen patients with presystolic liver pulsation in the absence of tricuspid stenosis. Some, but not all, of them also showed a prominent "a" wave in the jugular tracing. None of these patients had mitral valvular disease. The authors explain the strong presystolic pulsation in these cases as being due to resistance to right atrial outflow with reflux to the liver, caused by heart failure, right ventricular hypertension, pericardial effusion, pulmonary hypertension, and interatrial or aortic-atrial shunts.

These conditions must be kept in mind also in a consideration of the significance of venous presystolic pulsation in the neck, but we think that, in the presence of mitral valvular disease and in the absence of heart failure, the sign can be considered as almost pathognomonic of tricuspid stenosis.

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THE OCCURRENCE OF PERIPHERAL DEPOSITS OF LIPID IN ATHEROMATOUS PLAQUES OF ARTERIES

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SOME of the older descriptions of intimal lesions of atherosclerosis mention the frequent occurrence of a narrow zone of lipid at the edge of discrete intimal plaques. Benda[1] described deposits of fat embedded in fibrous tissue at the edges of old, well-formed, hyalinized or partly hyalinized plaques. This distribution is further emphasized in one of his drawings. MacCallum[2] stated that fat often forms "a yellow halo" around intimal lesions.

Numerous other descriptions of atherosclerotic lesions, however, do not refer to peripheral lipid deposits, probably because they do not occur with sufficient constancy to be considered a characteristic feature of plaque formation. Even when described, no adequate explanation has been offered for this particular, inconstant feature of the intimal lesion. It is possible, nevertheless, that if the significance of such deposits could be properly evaluated, information might be gained as to the mode of introduction of lipid into arterial plaques and to the mechanism by which the plaques themselves are formed. The present study was undertaken to investigate the chief features of the formation of marginal lipid deposits around old lesions.

GROSS CHARACTERISTICS

When sufficiently well developed to be detected on gross examination, the peripheral lipid appears as a distinct, narrow yellow ring or incomplete arc, usually less than 1 mm. in width, at or immediately adjacent to the raised edge of the plaque. The gross characteristics are best studied in the large expanse of intimal surface afforded by the aorta. Similar peripheral lipid accumulations may be identified about plaques in medium-sized arteries. In small arteries, when the lumen is greatly narrowed, lipid deposits are sometimes found at the proximal and distal edges of the occluding plaques. The lipid character of this peripheral zone is readily verified by staining of the gross specimens with dilute solutions of the Sudan IV followed by partial decolorization with 80 per cent alcohol. In the stained preparations, however, the lipid zone usually appears broader and less well defined than before staining.

At the margins of plaques in all stages of their development peripheral lipid deposits may be found. They are most readily detected at the edges of plaques that have sharp borders and that are partly or completely hyalinized. They may also be found at the periphery of completely calcified and even ulcer-

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ated lesions. It is likely, therefore, that these lipid accumulations bear no direct relationship to any one stage of plaque formation and cannot be considered as an early phase in the development of the main plaque itself.

Usually, in any one aorta, the peripheral rim of lipid does not occur as an isolated finding around a single lesion. In most instances either several or many plaques may have such deposits or none may show them. This is true even when the various plaques are in quite different stages of development. This suggests that the plaques themselves may play only a passive role in the formation of peripheral rings and that the accumulation of these secondary lipid deposits may depend upon conditions that are in effect throughout the vessel. In the aortas of persons of more than 40 years of age examined at necropsy at Bellevue Hospital, about one in every five reveals grossly visible lipid zones around intimal plaques.

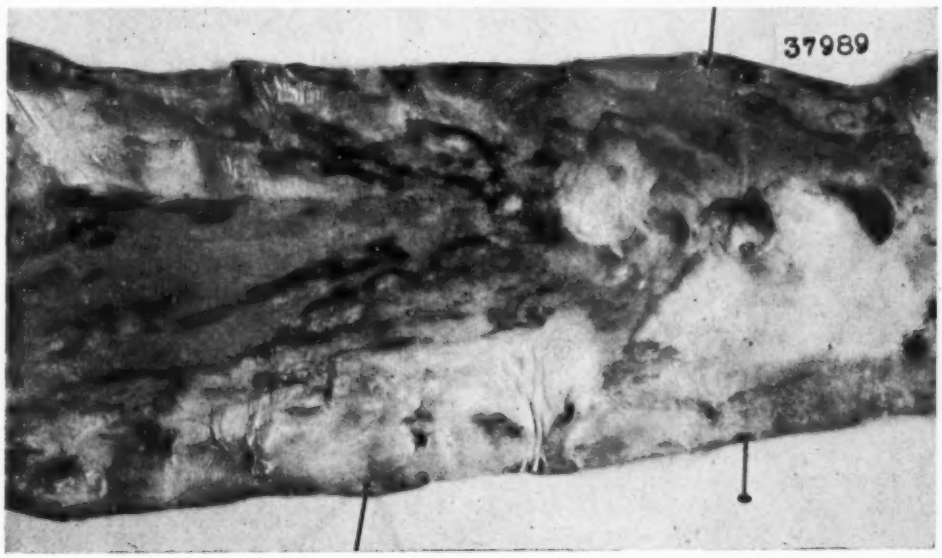

Fig. 1.—Photograph of intimal surface of lower descending thoracic aorta stained with Sudan IV. The posterior portions contain large, pearly gray, raised hyaline plaques that engulf the orifices of the intercostal arteries. The stained lipid deposits appear dark gray and are seen to outline the margins of the hyaline plaques in many areas. This is most pronounced where the plaques border upon the plaque-free anterior portion.

When large amounts of lipid in the form of streaks, patches, or widespread diffuse masses have been superimposed in the intima of an aorta that is already the seat of older, sharply defined plaques, distinct peripheral rings of lipid limited to the edges of the older plaques are not generally seen. The lipid patches themselves, however, often extend to and end abruptly at the margin of older plaques.

Marginal lipid deposits are most apt to form a complete encircling ring around plaques that are surrounded by wide areas of normal intima. When plaques are crowded together or partly coalescent, the borders that are in close proximity to adjacent plaques generally fail to show lipid deposits. In these same plaques, segments that impinge on normal areas of intima may have limited linear deposits of fat.

HISTOLOGIC CHARACTERISTICS

The peripheral mass of lipid has a fairly uniform microscopic appearance. It consists of aggregates of fat-laden phagocytes closely grouped together in interstices of otherwise compact fibrous tissue. Often the fat-laden cells are arranged in several parallel rows held apart by a few, thin connective tissue fibers. The mass of lipid-bearing cells is frequently sharply circumscribed; it may be triangular, wedge shaped, or partly elliptical in outline, but more often it is rather formless. It is usually lodged at the angle between the flat adjacent

Fig. 2.

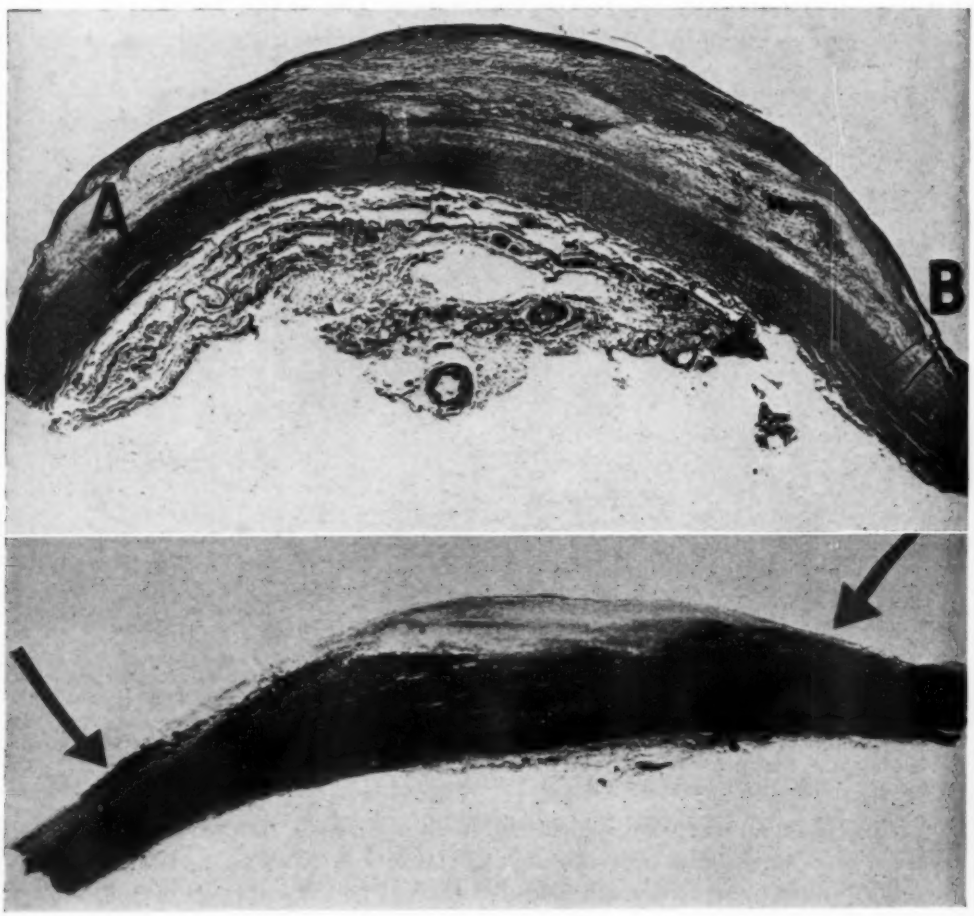

Fig. 3.

Fig. 2.—Low-power photomicrograph of a large aortic plaque, paraffin embedded and stained with hematoxylin and eosin. Lipid has been resorbed from the hyaline central portion, but there are laterally situated, newer deposits of lipid represented by the clear areas (*A*). At the left margin one of these fatty masses is directly continuous with the peripheral lipid deposit. On the right the other lipid mass has become separated from the small linear peripheral deposit (*B*) by a layer of fibrous tissue (×10).

Fig. 3.—Frozen section of an aortic plaque stained with Sudan IV. The dark discrete masses indicated by arrows are stained deposits of lipid. These are separated from the more centrally situated large fat depots.

intima and the elevated margin of the plaque. In polarized light almost all of the fatty material is doubly refractive.

In some instances the lipid mass tends to thin out at its own edges, and extensions of fat-laden cells are noted in the raised lateral fibrous wall of the plaques and in the adjacent intima bordering the plaque. Small nests of phagocytes and single ones may be slightly separated from the main mass and lie in adjacent

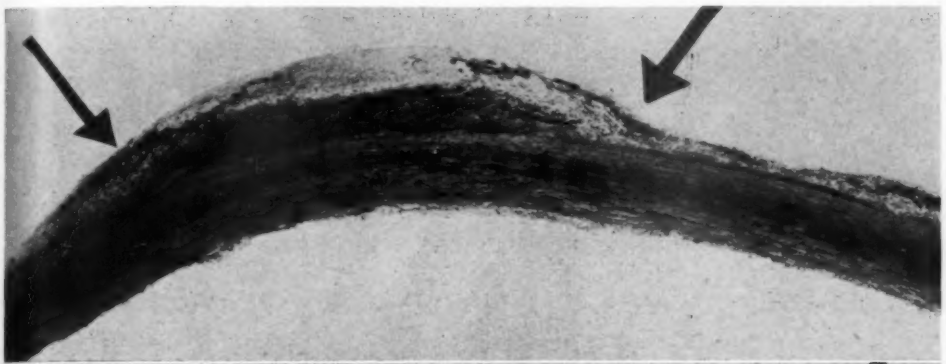

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4.—Frozen section of a partly hyalinized intimal plaque stained with Sudan IV. The peripheral lipid deposits indicated by the arrows extend in arclike streaks up the lateral border of the plaque but are detached from the deep central fatty mass. On the right the peripheral lipid is continuous with similar deposits in the adjacent thin intima.

Fig. 5.—Frozen section of intimal plaque stained with Sudan IV. A compact wedge of lipid is indicated by the arrow at the right margin. On the left border there is a large, more diffuse lipid mass similar to that noted in Fig. 2.

Fig. 6.—Frozen section of intimal plaque stained with Sudan IV. The arrows are directed toward small, loosely arranged, peripheral lipid masses lodged well beneath the surface in fibrous tissue but independent of the central lipid deposit. The peripheral lipid is apparently undergoing fibrous replacement, and the plaque has lost its rounded symmetrical contours.

connective tissue. In sections through small fibrous plaques a thin arc of lipid-containing cells continuous with thick wedges of fat at the periphery may bridge the entire plaque while the deeper portions of lesion are devoid of lipid.

In plaques that have a deep, centrally contained mass of atheromatous material, a thick layer of fibrous tissue often intervenes between it and the peripheral lipid zone. This in itself suggests that the peripheral lipid mass is an independent deposit and probably one that has occurred long after the central fatty mass was formed. It is not likely that in the organization of the original lipid mass by fibrous tissue replacement, nests of the initial deposit would be left at the periphery. Furthermore, the central lipid mass is usually in advanced stages of disintegration and the lipid is largely extracellular, whereas the fat-laden phagocytes external to the fibrous outer layer of the plaque are usually well preserved. There is no histological evidence that the peripherally situated deposit represents fat that is being removed from deeper portions of the plaque. There are no planes of cleavage in the fibrous shell along which fat-laden cells could penetrate from the interior of the plaque.

In earlier, lipid-rich plaques with a relatively thin outer shell of fibrous tissue, peripheral accumulations of fat-laden phagocytes are often in more or less direct continuity with central extracellular deposits of atheromatous material. This can be interpreted as evidence that lipid continues to be fed into the central mass of a plaque as long as its edges remain unprotected by a layer of fibrous tissue. In many plaques the fat-laden phagocytes are continuous with the central lipid mass at one edge after the other edge is sealed off (Fig. 5). Less commonly (Fig. 2), masses of extracellular lipid may be found eccentrically within large plaques after the central deep portion has undergone considerable fibrosis. These eccentrically situated lipid masses may still be in contact with peripheral intracellular lipid. This finding suggests an explanation for the formation of new lipid plaques that are often superimposed at the edges and partly coalescent with older, more fibrous plaques.

Blood vessels are not found within or in the vicinity of the peripheral lipid zone. On the contrary, old plaques that are vascularized at their margins seldom show peripheral lipid zones. Cholesterol crystals or other evidences of deterioration, such as secondary inflammatory changes, are not found in the marginal lipid, indicating that it is a new, recent deposit. In some instances, however, the fat-laden cells may appear shrunken or collapsed, indicating that their fatty contents may have been resorbed. Occasionally, groups of fibroblastic cells are found among the fat-laden cells, suggesting that a gradual fibrous transformation may occur without vascularization.

Histologic sections of intimal plaques often reveal small peripheral accumulations of lipid that were not apparent on gross examination. The incidence of this feature of atherosclerosis is thus much higher than would be suspected from gross inspection of the lesions. In frozen sections of fifty intimal plaques from twenty aortas stained with Sudan IV, either one or both edges of twenty-six of the lesions were found to have discrete lipid masses. The gross observation that peripheral lipid masses tend to occur around several or none of the plaques in any particular vessel was further borne out. Thirteen of the plaques that

failed to show peripheral lipid were taken from five aortas. In thirteen plaques from six other aortas both edges of each plaque had marginal zones of lipid. In the remaining twenty-four plaques from nine aortas some plaques showed peripheral lipid while others failed to do so, but even in these, the peripheral lipid was either scanty or abundant in most of the plaques obtained from a single vessel.

DISCUSSION

The margins of old intimal plaques appear to be particularly favorable areas for the accumulation of lipid-containing phagocytes in much the same fashion as the regions surrounding arterial branches are select sites for early lipid streak formation. If these accumulations represent secondary or new deposits

Fig. 7. Fig. 8.

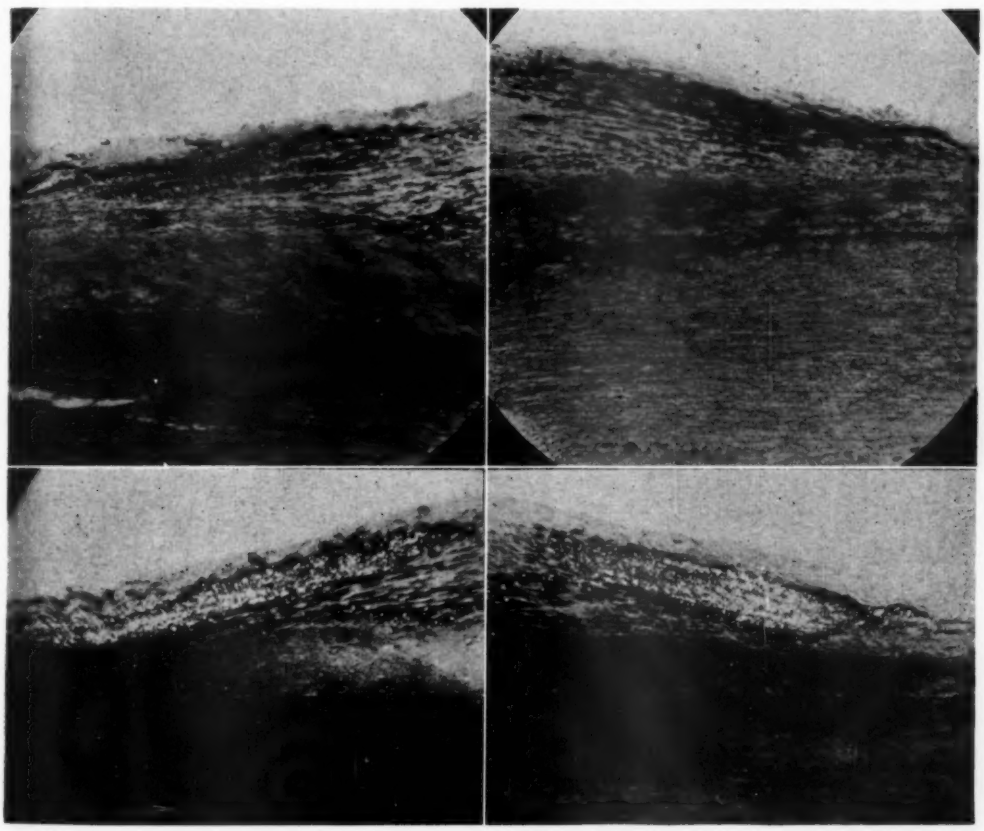

Fig. 9. Fig. 10.

Figs. 7 and 8.—Frozen section of edges of large hyalinized intimal plaques stained with Sudan IV. The peripheral lipid appears as darkly stained material lodged in crevices between connective tissue fibers so that it appears in places as narrow streaks arranged in parallel fashion.

Figs. 9 and 10.—Photomicrographs in polarized light of frozen sections stained with Sudan IV. Doubly refractive lipid appears as finely spotted white granules. It may be seen that the bulk of the peripheral lipid deposits is anisotropic.

of lipid that may undergo fibrous transformation, a mechanism is suggested by which individual intimal plaques may continue to enlarge in a progressive fashion. It is improbable that new lipid can reach the central, deep, fatty portion of old

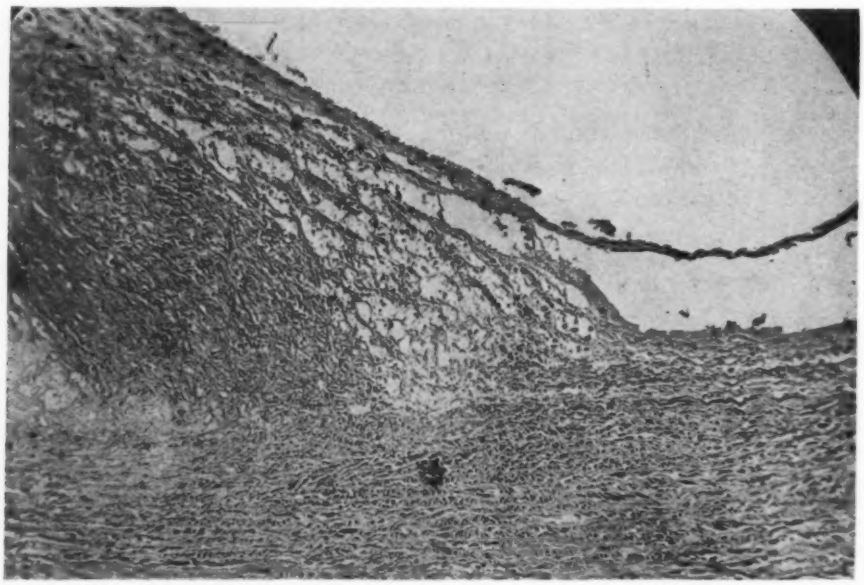

Fig. 11.—Paraffin-embedded, hematoxylin-eosin stained section through the edge of a large fibrous intimal plaque. The characteristic position and wedge shape of the peripheral fat deposit may be seen (×86).

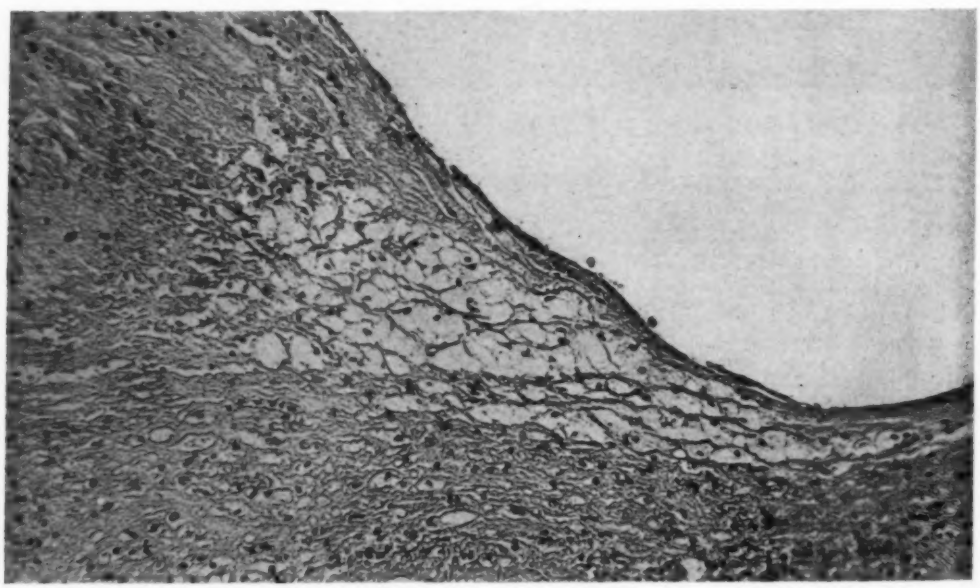

Fig. 12.—Paraffin-embedded, hematoxylin-eosin stained section through the margin of an intimal plaque. A cluster of large, vacuolated, lipid-containing phagocytes is seen just beneath the endothelium at the edge of the plaque (×153).

plaques once it has become enclosed by an outer shell of hyalinized connective tissue. Since plaques tend to increase in size as well as in number with advancing age, it is probable that some mechanism is in operation by which this progression can occur.

In previous reports it has been claimed that intimal lipid tends to collect at natural points of anchorage and relative immobility[3] or at artifically produced areas of fixation[4] in arterial walls due to the massaging action of the pulse movements of the vessel. According to this theory, the areas in which discrete lipid masses ultimately come to rest may not represent the points at which the lipid was initially introduced into the intima because of increased local permeability. On the contrary, it is contended that the initial deposits of lipid may be widely disseminated throughout the intima. During periods of active deposition, the diffusely dispersed lipid may be gradually displaced from the more actively contracting portions of the vessel wall toward the points of adventitial anchorage and relative fixation. If periods of active resorption of lipid occur, the still dispersed remnants of lipid in the more freely contracting portions of the vessel should be more readily resorbed than that which has already collected in large depots at areas of fixation. Thus, the localized nature of atheromatous lesions can be attributed, according to this thesis, to a process of rearrangement of lipid within the intima under the influence of rhythmic arterial pulsations. The thin streaks and broad patches of lipid seen so frequently at all ages in the aorta can be considered as deposits in the active process of transformation from the diffuse to the localized variety.

By applying this theory, a simple explanation for the occurrence of peripheral lipid deposits at the margins of old arterial plaques can be given. Fibrous plaques represent secondary, newly acquired foci of relative immobility and fixation in the pulsing vessel wall. Lipid deposited subsequently in the surrounding intima is redirected in its gradual displacement toward the perimeter of old hyalinized plaques. This movement can be effected whether the lipid is extracellular or within wandering unattached phagocytes.

Almost every investigator, including Askanazy,[5] Klotz,[6] Aschoff,[7] and Leary,[8] who has studied the formation of lipid streaks in the arterial intima, has concluded that they are often of a transient character. During periods of active lipid resorption, lipid is probably more readily dislodged from the thinly dispersed deposits that still remain in the freely contracting portions of the vessel than from the larger lipid aggregates that have reached the sheltering edge of a fibrous plaque. In this fashion relatively persistent masses of fat may be formed around the margins of old lesions and be retained after the diffusely dispersed lipid has disappeared.

This interpretation would account for the special attributes of marginal lipid formation already noted. It would explain the occurrence of these zones around old plaques in all stages of development since the only role of the plaque in the process is to provide a small unyielding focus in an otherwise freely moving medium. It would account for the occurrence of marginal lipid zones around many plaques in an aorta rather than around single plaques since their formation depends upon alternating periods of lipid deposition and resorption throughout

the vessel as a whole rather than at restricted areas. Finally, it would account for the development of peripheral lipid masses at margins of plaques that border on expanses of plaque-free intima and the absence of such deposits around plaques that are in close proximity. Where there is little intervening flat intima there would be little opportunity for the movement of lipid droplets toward the fixed areas occupied by plaques.

SUMMARY

Localized collections of fat-laden phagocytes occur with sufficient frequency at the edges of old intimal plaques to indicate that these areas are particularly susceptible to new lipid deposits. It is suggested that the fibrous replacement of such peripherally situated masses of lipid is the chief method by which old plaques may continue to undergo progressive enlargement.

Analysis of the main characteristics of the marginal lipid deposits favors the view that their accumulation depends upon the anchoring and immobilizing effects of the previously formed fibrous plaque rather than upon any special, localized increase of permeability to lipid. It is further hypothesized that these zones of lipid are formed by a gradual movement and collection of diffusely dispersed lipid displaced from the intimal tissue adjoining the plaques under the impetus of arterial pulsations and that such periatheromatous masses, by reason of their bulk and relatively protected situation, are more resistant to resorption than scattered streaks and patches of lipid.

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SUBACUTE BACTERIAL ENDOCARDITIS

Report of a Case With Recovery From Reinfection After Thirty-two Months

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THE introduction of penicillin therapy in the treatment of subacute bacterial endocarditis in 1943 and 1944 has resulted in the recovery of 60 to 80 per cent of the patients. Associated with the increased survival rate with modern antibiotic therapy, several problems have become increasingly important with respect to the management and sequelae of this disease. These problems may be classified into two groups: (1) diagnosis and therapy and (2) sequelae and complications.

Grossman and Katz,[18] Mokotoff, Brams, Katz, and Howell,[2] and Jones and Tichy[1] have emphasized the importance of early diagnosis and early institution of therapy not only from the point of view of controlling and eradicating the focus of infection but also in minimizing the further damage to the endocardium. Mokotoff, Brams, Katz, and Howell,[2] Christie,[3] and Henry[4] have stressed the necessity for intensive and prolonged therapy in preventing reactivation. Mokotoff and co-workers,[2] Snyderman and Tipping,[5] Henry,[4] and Orgain and Donegan[6] have pointed out the importance of determining the in vitro sensitivity of the organism and checking the penicillin blood levels during the course of therapy. Orgain and Donegan[6] could find no significant correlation between the route of administration of penicillin and the percentage of cures. As a result of such work it is evident that inadequate blood levels of penicillin or inadequate length of therapy may lead to increased resistance of the organism or to reactivation of the infection when therapy is stopped prematurely.

Grossman and Katz,[18] in a recent review of the therapy of subacute bacterial endocarditis, have emphasized the importance of determining the sensitivity of the organism, have stressed the necessity of maintaining a penicillin blood level five to ten times that of the in vitro sensitivity, and have recommended that penicillin therapy be maintained for at least three weeks after the subsidence of symptoms and after the blood culture has become negative. They also called attention to the fact that penicillin blood levels should be as nearly continuously maintained at the desired therapeutic range as possible. Grossman and Katz further pointed out that reactivation of the infection is due either to inadequate plasma levels or to the early discontinuance of treatment.

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On the other hand, patients adequately treated may have a recurrence of symptoms at a later date. When a different organism is present at the time of the second episode or when a symptom-free period longer than one year and associated with negative blood cultures has been present, then this second episode is more properly classed as a reinfection even if the organism be indistinguishable from that originally present.[7] Seven such cases of recovery from a reinfection, in contradistinction to a reactivation, have been reported: (a) an initial infection with *Streptococcus faecalis* followed in five and one-half months by reinfection with *Streptococcus viridans*[3]; (b) reinfection after six months[8]; (c) and (d) reinfection after one year[9,10]; (e) reinfection after twenty months[7]; (f) reinfection after thirty-one months[11]; and (g) initial infection due to *Staphylococcus aureus* followed in one year by an infection with micro-aerophilic streptococcus and followed by a third attack in six months due to *Str. viridans*, all cured by penicillin.[12]

Another major problem presently in the foreground is the residue of 30 per cent fatalities still occurring in the cases under antibiotic therapy. Kaplan, Rosenman, Katz, and Brams[15] studied a group of eighteen patients following recovery from infection for twenty-five months to sixty-one months. Three of their patients died in congestive heart failure. Three others were living but exhibited progressive heart disease. All patients with heart failure, both living and dead, had exhibited dynamically significant aortic regurgitation. In each instance, these effects were attributable to the course of the subacute bacterial endocarditis. Pillsbury and Fiese[11] have recently reported a follow-up study of a series of thirty patients cured with penicillin. In their group there were ten deaths (33 per cent); eight were due to heart failure, one to carcinoma, and one to a cerebrovascular accident. There was one case of reactivation and one case of reinfection. Eight living patients exhibited major embolic phenomena. Disregarding the incidental causes of death, neoplastic and degenerative diseases which may become increasingly important as the duration of survival is greater and as more and more patients come to fall into the older age groups, the major sequelae of subacute bacterial endocarditis are (a) heart failure, (b) embolic phenomena, and (c) reinfection.

Myocardial failure may be precipitated in healing and healed cases of subacute bacterial endocarditis by one of several mechanisms. In the course of healing of an ulcerated valve, greater valvular deformity than was present prior to the infection may result.[13,14] Such changes may lead to an increased load against which the myocardium must operate. Saphir and Leroy[14] have shown that true aneurysms of the valve leaflets may result from subacute bacterial endocarditis in the healing or healed stage. Some of these have been shown to rupture and lead to valvular insufficiency, and a dynamically significant increment of insufficiency may be enough to impair the myocardial function as shown by Kaplan, Rosenman, Katz, and Brams.[15] Clinically, however, aortic insufficiency is by far the most important lesion.[15] Paradoxically, these aneurysms are morphological evidence of healing, and clinical cures yet may so embarrass the myocardium as to lead to heart failure.[14,15] Saphir and Leroy[14] have been unable to find a single instance of true aneurysms in necropsy specimens prior to the era

of antibiotic therapy. Instead, false aneurysms consisting of thrombi in various stages of organization which push part of the valve leaflet have been present. Such lesions may well have been of little dynamic consequence in as much as no correlation between their occurrence and heart failure has been found.

Saphir, Katz, and Gore[16] have recently analyzed a large series of cases of subacute bacterial endocarditis and correlated the morphology of myocardial lesions, clinical history, and electrocardiographic changes. They have demonstrated that the myocardium may be involved by (a) diffuse and focal myocarditis, (b) perivascular fibrosis, (c) bacterial and calcific emboli, (d) focal areas of infarction, and (e) granulomatous myocarditis secondary to calcific emboli. They have stressed the clinical and electrocardiographic evidence of such changes present during life and pointed out that these changes may lead to impairment of the myocardium and failure. Saphir[17] called attention to the fact that calcific emboli and myocardial granulomas secondary to them occur only in healing and healed endocarditis. He could find no instance of such changes in necropsy material prior to the sulfonamide and antibiotic era.

A case illustrating these problems is presented.

CASE REPORT

A 66-year-old white woman was admitted to this hospital complaining of a 7 pound weight loss during the preceding four months, low-grade fever of one month's duration, and fatigue. Past history disclosed a gastroenterostomy performed thirty-six years earlier for duodenal ulcer and a ruptured ectopic pregnancy two years later. Thirteen years prior to this admission, diagnoses of rheumatic, hypertensive, and arteriosclerotic heart disease were entertained because of cardiac enlargement, a harsh precordial systolic murmur, and a blood pressure of 190/100 mm. Hg. At that time, she had dyspnea, palpitation, and precordial pain at rest. At the age of 62 years she developed ankle edema which responded rapidly to bed rest and digitalization. She was hospitalized four times in the next four years with episodes of mild cardiac failure (moderate dependent edema, hepatomegaly, and scattered moist râles at both lung bases). In each instance, response to therapy was excellent. Repeated electrocardiograms were definitely abnormal, compatible with chronic coronary insufficiency.

Physical examination at this admission revealed an emaciated woman weighing 105 pounds. The temperature was 98.6° F. and the blood pressure 145/70 mm. Hg. A harsh precordial murmur was present, systolic in time and loudest at the apex. P_2 was accentuated and greater than A_2. The left heart border was percussed at the anterior axillary line in the fifth interspace. The liver was slightly enlarged and not tender. The spleen could not be palpated. Laboratory data revealed: red blood count 3,540,000; white blood count 13,550; sedimentation rate 34 mm. per hour; hemoglobin 11.5 mg. per cent. Urinalysis showed a specific gravity of 1.015 to 1.020, a faint trace of albumin, and occasional red and white cells in the sediment. The electrocardiogram showed minor nonspecific changes when compared to the previous record. A blood culture, on admission, was positive for *Str. viridans* with a sensitivity to penicillin of 0.156 Oxford units per cubic centimeter.

Therapy with penicillin, 50,000 units intramuscularly every three hours, was instituted. The penicillin level was thus maintained between 1.25 and 1.56 Oxford units. On the twentieth day penicillin was stopped in view of six consecutively negative blood cultures. Six days later. *Str. viridans* was again isolated from a blood culture, and penicillin in the same dosage was again employed. Because of two subsequent positive blood cultures and failure of the penicillin level to rise above 0.80 Oxford units, the dosage was increased to 75,000 units every three hours. A level of 5.12 Oxford units was thus maintained, and repeated blood cultures were sterile. There was no change in the cardiac findings. The patient improved with a marked weight gain and

no longer was fatigued. On the seventy-second hospital day the penicillin was discontinued and the patient discharged. The total dosage was 26,375,000 units of penicillin.

Thirty-two months later, the patient was again admitted complaining of generalized malaise, low-grade fever of fifteen days' duration, and a 5 pound weight loss during the preceding two weeks. She had been well since her preceding admission except for occasional mild episodes of dyspnea, palpitation, and precordial pain. Vague gastrointestinal symptoms had led to two gastrointestinal series both reported negative. Repeated blood cultures had been negative. Physical examination at this time was essentially the same as on the last admission except for a blood pressure of 200/90 mm. Hg and temperature of 102.2° F. Laboratory data were similar to those of the previous admission. Blood cultures on the first three days were positive for *Str. viridans* which was sensitive to 0.15 Oxford units of penicillin. Therapy was instituted with penicillin, 300,000 units every twelve hours intramuscularly. The resultant blood level was 2.5 to 3.2 Oxford units until the thirty-eighth hospital day when a level of 1.6 Oxford units was reported. The dosage was increased to 300,000 units in the morning and 600,000 units at night; this was effective in maintaining a blood level of 2.5 to 3.2 Oxford units. All subsequent blood cultures were negative, and the temperature returned to normal on the second day. The cardiac status remained unchanged. Recovery was without incident, and she was discharged on the fifty-fifth hospital day, a total of 34,500,000 units of penicillin having been administered.

Weekly blood cultures continued to be sterile, and the general condition was unchanged until four weeks after discharge. At this time, there was a sudden onset of severe headache folfollowed by the development of acute pulmonary edema and coma. She was again admitted to the hospital. Physical examination revealed an elderly emaciated woman in coma. The pulse was 160, temperature 106.4° F. (rectal), and blood pressure 105/85 mm. Hg. There were many coarse and moist râles throughout the lung fields. Flaccid paralysis of the extremities was present. The patient's condition grew worse, and she died several hours after admission without regaining consciousness.

At necropsy* the heart weighed 460 grams. The walls of the right and left auricles and the right ventricle were hypertrophied. The endocardium covering the mitral valve and the left auricle was thickened and opaque, and the chordae tendineae were thickened, shortened, and fused. The leaflets of the mitral valve were thickened and fused with the formation of three true aneurysms of the mitral valve by fusion of the edges and out pouchings of the thinned-out leaflet toward the auricular surface. Foci of irregular nodular calcification of the mitral valve, especially the aortic leaflet, were present, covered by endocardium. Microscopically, moderate coronary atherosclerosis was present as well as calcific emboli in several of the smaller coronary arteries in the myocardium. Foci of fibrosis were present throughout the myocardium. Microscopic examination of the mitral valve revealed a healed endocarditis of the rheumatic type with evidence of a superimposed healed ulcerative endocarditis (focal proliferation of fibrous tissues, vascularization, and deposition of calcium and fibrin covered by endocardium).

Multiple and massive intracerebral hemorrhages were present. The cerebral vessels were markedly narrowed and sclerotic, but no evidence of thrombi or emboli was found. The kidneys revealed moderate arterial and arteriolar nephrosclerosis.

An incidental finding consisted of a small polypoid carcinoma of the ascending colon.

Death was due to massive intracerebral hemorrhages, most probably based on arteriosclerotic vascular disease. Inasmuch as the valvular lesions were entirely healed and no cerebral emboli were found and since extensive cerebral arteriosclerosis was present, it was felt that the endocarditis played no role in the terminal episode.

DISCUSSION

This case illustrates several of the factors presented above. In the first episode of subacute bacterial endocarditis, therapy was stopped too soon (on the twentieth day) and had to be reinstituted six days later when the blood culture again became positive. It is evident that the total dosage and the duration

*Performed by Dr. Otto Saphir, Chicago, Ill.

of therapy are prime factors in effecting a cure. Inadequate therapy may lead to reactivation as has been stated by Grossman and Katz[18] and Christie.[3] On the other hand, it is highly unlikely that the amount of penicillin previously given to a patient with cured subacute bacterial endocarditis bears any relationship to a reinfection. A "cured" patient is just as susceptible to another infection as he would have been had only the antecedent rheumatic valvulitis been present.

The necessity of repeated penicillin blood levels and sensitivity studies is well illustrated in this case.[2,5,19] In both episodes of infection, it was necessary to increase the penicillin dosage by one-third because of inadequate blood levels. Schlichter, MacLean, and Milzer[19] have recently recommended a direct test for determining the therapeutic value of penicillin levels by assay with the strain of bacteria isolated from the patient. It is thus possible to determine whether the penicillin level present in the plasma is sufficient to inhibit completely the growth of the patient's own organism.

Early institution of therapy is important in preventing progressive deformity of the endocardium and valves.[1,15,18] The aneurysms speak for the deformity following ulceration present in this case. However, they did not rupture nor is any evidence present that they led to hemodynamically significant changes, either a greater degree of stenosis or insufficiency. At necropsy two of the myocardial lesions associated with healed subacute bacterial endocarditis were found: perivascular fibrosis and calcific emboli. In healed cases of subacute bacterial endocarditis, as the time of survival is lengthened and the patients reach the older age groups, it will become increasingly important to watch for superimposed degenerative and neoplastic disease.

SUMMARY

1. A discussion of some of the factors in therapy necessary for the cure of subacute bacterial endocarditis is presented. The sequelae of subacute bacterial endocarditis leading to death in the bacteria-free stage are also discussed.

2. A case report is presented in which there was recovery from a reinfection contracted thirty-two months after the initial episode of subacute bacterial endocarditis. The interval between the initial episode and reinfection is the longest on record.

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UTILITY AND LIMITATIONS OF INTRAVENOUS QUINIDINE IN ARRHYTHMIAS

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THE development of a colorimetric analytical procedure for the determination of plasma quinidine concentration has helped to establish a more precise basis for its use in cardiac arrhythmias. It has been established that the dose of quinidine ordinarily employed is far too small to attain blood levels of 4 to 9 mg. per liter, which are usually necessary to effect conversion to normal rhythm.[2,3] It is necessary that 0.4 to 0.6 Gm. of quinidine be given every 2 hours for 5 doses to achieve such concentrations,[2] although there is considerable individual variation in the blood levels of quinidine when it is given orally.[4-7] This, together with the varying dosage schedules in common use, is one of the factors contributing to divergent experience and opinions regarding the value of quinidine in the management of disorders of the cardiac rhythm. Furthermore, the effect of oral quinidine is often difficult to evaluate because of the spontaneously transient nature of many arrhythmias. The rapidity of action of intravenous quinidine facilitates study of the pharmacological properties of the drug and permits a more definitive evaluation of its therapeutic efficacy.

This report comprises a study of 44 subjects with arrhythmias treated with intravenous quinidine. These included 32 consecutive unselected patients with various types of acute paroxysmal arrhythmias and twelve selected patients with chronic auricular flutter or fibrillation, or extrasystoles. Quinidine lactate in ampules of 10 c.c. containing 0.65 Gm. was used.* Initially the drug was given in fractionated doses of 0.06 Gm. every 3 minutes. This dosage schedule was later modified so that the majority of patients received 0.13 Gm. every 5 minutes. If the arrhythmia was not brought under control after a total of 0.65 Gm. was given in this manner, further administration was discontinued. In a few patients in the absence of contraindications, further 0.3 Gm. doses were given if necessary at ½ to 1 hour intervals.

Electrocardiograms were recorded throughout the entire trial period, employing the direct writing Sanborn Viso-Cardiette. The tracings were obtained at the time of injection of each fractional dose and at brief intervals after each dose, or whenever a change in the character of the tracing was thought to have occurred as indicated by the stylus movement. Usually Lead II or CR_1 was utilized, as auricular activity is best recorded in these leads.

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RESULTS

The findings may be analyzed in terms of efficacy in terminating arrhythmias and toxicity.

I. Efficacy.—In 22 of the 44 patients treated, the arrhythmia was successfully terminated; in 22 quinidine was ineffective. Several factors were found to bear significantly on the therapeutic outcome.

A. Duration of arrhythmia: In 16 patients the arrhythmia was of a chronic nature. In none of these did conversion to sinus rhythm occur. In 28 patients the arrhythmia was acute (less than 2 days in 25, and 3 days, 6 days, and 3 weeks in the remaining patients). Conversion to sinus rhythm occurred in 22 of these 28 patients. In 1, temporary restoration of normal rhythm occurred twice. There was failure to convert to normal rhythm in 5 cases (digitalis toxicity, 2 cases; hypertensive heart disease and cardiac failure with shock and coma, 1 case; rheumatic heart disease with enlarged left auricle, 1 case; hypertensive heart disease uncomplicated, 1 case). The relationship of the duration of the arrhythmia to success or failure with quinidine administration was quite striking.

B. Type of arrhythmia: The effectiveness of quinidine did not appear to have any clear-cut relationship to the type of arrhythmia. Restoration of normal rhythm occurred in 9 of 18 cases of auricular fibrillation, in 6 of 15 cases of auricular flutter, in both of 2 cases of supraventricular tachycardia, in 4 of 7 cases of ventricular tachycardia, and in neither of 1 case each of paroxysmal ventricular fibrillation and persistent ventricular extrasystoles.

C. Type of heart disease: Restoration to sinus rhythm occurred in 10 of 16 subjects with no other definite evidence of organic heart disease. Included in this group were 5 patients with essential hypertension, and 1 case each of thyrotoxicosis, asthma and pulmonary fibrosis, diabetic acidosis, bronchiogenic carcinoma with pericardial effusion, and lobar pneumonia. In 6 patients no factor was found which might have been responsible for the arrhythmia. Successful conversion to sinus rhythm occurred in 5 of these 6 patients. In 4 cases of acute myocardial infarction, the arrhythmias were terminated by quinidine (auricular fibrillation, 3 cases; ventricular tachycardia, 1 case). Four patients with auricular flutter secondary to mitral stenosis were treated with intravenous quinidine. Restoration to sinus rhythm was effected in only 1 of the 4 patients. One patient with auricular flutter reverted to sinus rhythm temporarily on 2 occasions, but the arrhythmia recurred after 5 and 10 minute periods of sinus rhythm.

In contrast to the high degree of success with quinidine in arrhythmias occurring in the absence of significant organic heart disease was the almost regular failure of quinidine in subjects with enlarged hearts who were in congestive failure. Of 13 subjects with congestive failure due to hypertensive and arteriosclerotic heart disease, quinidine restored sinus rhythm in only 2, and in 1 of these subjects further progressive changes in the form of atrioventricular dissociation with ultimate cardiac standstill and death occurred after the arrhythmia (ventricular tachycardia) was broken.

D. Dosage: In 11 of the 22 patients who responded successfully to quinidine, the arrhythmia was terminated by 0.26 Gm. or less. In 5 of these patients

reversion to sinus rhythm occurred within 1 minute after 0.13 Gm. of intravenous quinidine. Only 4 patients required 0.65 Gm. or more; 1 of these was a subject with hypertensive heart disease and enlarged heart, another had acute anterior wall myocardial infarction, and the other 2 had arrhythmias due to digitalis toxicity. In the patients failing to respond to quinidine, 0.13 Gm. doses at 5 minute intervals up to a total of 0.65 Gm. were usually employed. Three subjects received a total of 1.17, 1.94, and 2.40 Gm., respectively, without restoring sinus rhythm.

E. Previous digitalization: Of the 22 patients responding to quinidine, 16 had not received digitalis, and 1 only 0.4 mg. of digitoxin a few hours previous to administration of quinidine. Ten of the 22 patients failing to respond to quinidine were fully digitalized. These observations offer no evidence that previous digitalization enhances the therapeutic effect of quinidine.

II. Toxicity.—

A. Symptoms: Untoward subjective reactions developed in 14 subjects. These consisted of nausea (7), vomiting (3), cramps (4), urge to defecate or urinate (4), and cold sweat and apprehensiveness (7). Such symptoms were unrelated to dosage and occurred with as little as 0.13 to 0.26 Gm.

B. Ballistocardiographic effects: In view of the effects of quinidine on the electrocardiogram and the widespread opinion that quinidine is a cardiotoxic drug, it was considered of interest to investigate its influence on the dynamics of cardiac ejection. Serial ballistocardiograms were made in 4 normal subjects following intravenous injection of quinidine lactate in graduated 0.13 Gm. doses at 5 minute intervals until a total dose of 0.65 Gm. had been given. In no instance was there any demonstrable change in the ballistocardiogram. There was no decrease of amplitude nor any lag in the J wave such as might have been anticipated if the velocity of ejection had decreased. The duration of systolic ejection, as measured in simultaneously recorded arterial sphygmograms, was unaffected, as was the isometric phase of systole, employing as a relative index the interval from the onset of the QRS complex to the I wave of the ballistocardiogram. The heart rate and blood pressure were not significantly altered. In all 4 subjects typical electorcardiographic changes occurred, i.e., lengthening of the Q-T interval (electrical systole) and T-wave abnormalities.

The findings suggest that changes in electrical activity of the heart are not necessarily accompanied by alterations in cardiac dynamics and that quinidine in doses which cause significant electrocardiographic abnormalities does not alter the mechanics of cardiac ejection. Ferrer and associates[8] in a recent study found no significant change in circulatory dynamics produced by quinidine other than peripheral vasodilatation in 20 patients in whom a variety of cardiac functions was investigated by the right heart catheterization technique.

C. Arrhythmias produced by quinidine: Serious arrhythmias resulting from quinidine occurred in 5 cases leading to death in 4 subjects. In 2 of the fatal cases, quinidine was given because of arrhythmias due to digitalis toxicity. The following are brief summaries of the 4 cases where death appeared to be related to quinidine administration and an additional case in which serious toxicity appeared to be associated with quinidine administration.

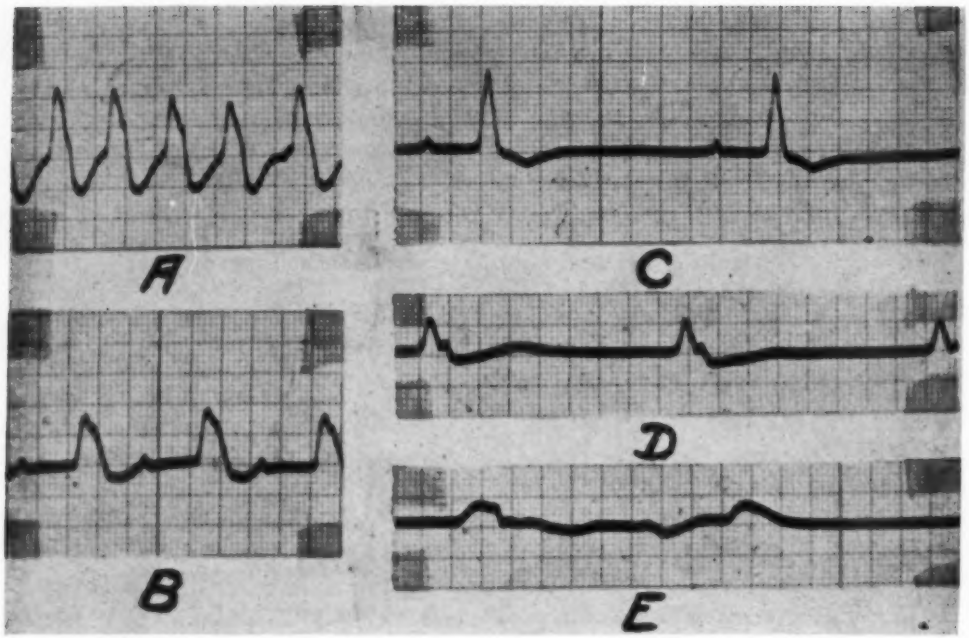

Fig. 1. (Case 1).—Cardiac standstill. *A*, Initial tracing; *B*, 42 minutes after last dose (0.65 Gm. in all); *C*, 75 minutes after last dose; *D*, continuation of *C*; *E*, continuation of *D*.

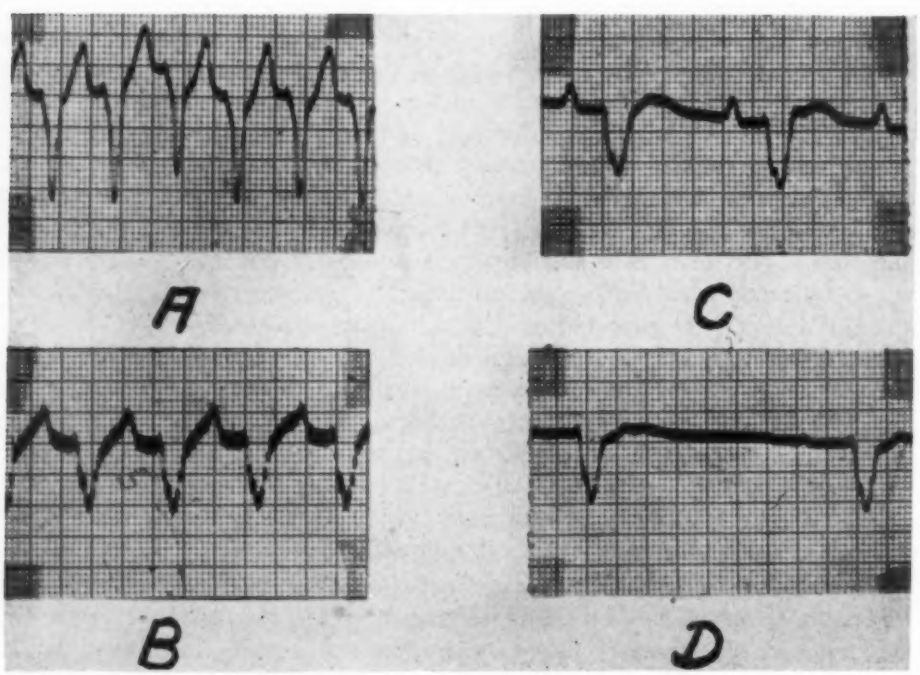

Fig. 2. (Case 2).—Cardiac standstill following quinidine (Lead II). *A*, Initial tracing; *B*, 5 minutes after 0.13 Gm. intravenously; *C*, 2 minutes after 0.26 Gm. intravenously; *D*, continuation of *C*.

CASE 1.—Lanatoside C(0.8 mg. Cedilanid) was given intravenously to a 66-year-old man with hypertensive heart disease with pulmonary edema. A few minutes later ventricular tachycardia developed. Quinidine lactate was given in 0.13 Gm. fractionated doses to a total of 0.65 Gm. Forty-two minutes after the total dose of 0.65 Gm. the ventricular rate slowed and sinus rhythm was restored. Increasing bradycardia and lengthening of the P-R interval developed. This progressed to idioventricular rhythm with cardiac standstill and death 75 minutes after the last dose of quinidine. Autopsy showed left ventricular hypertrophy, focal myocardial fibrosis, bicuspid aortic and pulmonary valves, and calcification of the aortic valve (Fig. 1).

CASE 2.—A woman, 50 years old, with hypertensive heart disease and coronary insufficiency, on a maintenance dose of digitalis developed ventricular tachycardia following an automobile accident. Five minutes after 0.13 Gm. of quinidine was given intravenously the ventricular rate slowed from 146 to 107 per minute with widening of the QRS complex. Immediately after an additional 0.13 Gm. was given, sinus rhythm, rate 62 per minute, was present, and the P-R interval became prolonged with further widening of the QRS complex. This progressed to complete cardiac standstill and death 7 minutes after the last dose was given (Fig. 2).

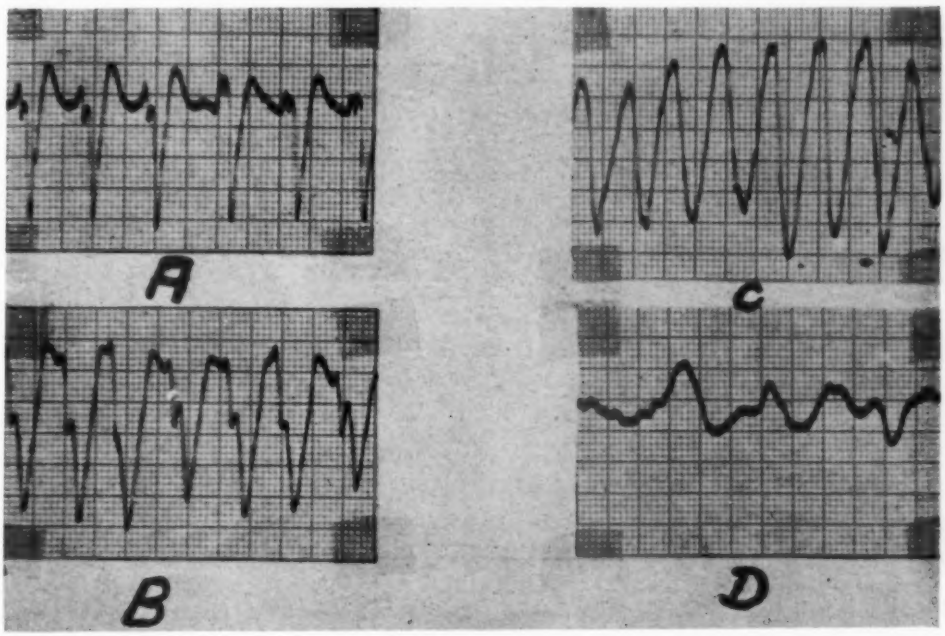

Fig. 3. (Case 3).—Ventricular fibrillation following quinidine (Lead III). *A*, Initial tracing; *B*, 27 minutes after the first dose (0.13 Gm. intravenously), 1 minute after a total of 0.39 Gm. had been given; *C*, continuation of *B*; *D*, continuation of *C*.

CASE 3.—A woman, 50 years old, with hypertensive heart disease and chronic congestive failure was hospitalized for ventricular tachycardia provoked by overdigitalization. The arrhythmia was of ten hours' duration when quinidine was given. Twenty-seven minutes after the first 0.13 Gm. and 1 minute after a total of 0.4 Gm. had been given, the QRS complexes widened, ventricular fibrillation developed, and the patient died. Autopsy revealed cardiac hypertrophy, pulmonary edema, chronic passive congestion of the lungs and liver, nephrosclerosis, and arteriosclerosis (Fig. 3).

CASE 4.—A man, 60 years old, with hypertensive heart disease on maintenance dosage of 0.1 mg. of digitoxin daily was hospitalized in coma with pulmonary edema and advanced right

heart failure. Auricular fibrillation, ventricular rate 150 per minute, with incomplete right bundle branch block was present. A single 0.65 Gm. intravenous dose of quinidine was given, with almost immediate widening of the QRS complex, progressive cardiac slowing, and idioventricular rhythm leading to complete cardiac standstill. Convulsions developed and the patient died (Fig. 4).

CASE 5.—A 65-year-old man was hospitalized in congestive failure due to hypertensive and arteriosclerotic heart disease. Auricular flutter with a ventricular rate of 230 per minute was present. One minute after a total of 0.4 Gm. of quinidine had been given in fractional 0.13 Gm. doses, the ventricular rate decreased to 107 per minute with marked slowing of the auricular circus movement. Seventy-six minutes after a total of 0.65 Gm. had been given, the patient suddenly developed multifocal ectopic ventricular beats with runs of ventricular tachycardia, rate 240 per minute, and a convulsive seizure. The ventricular tachycardia lasted for an hour, and the rhythm then reverted to auricular flutter. Death occurred 20 hours later.

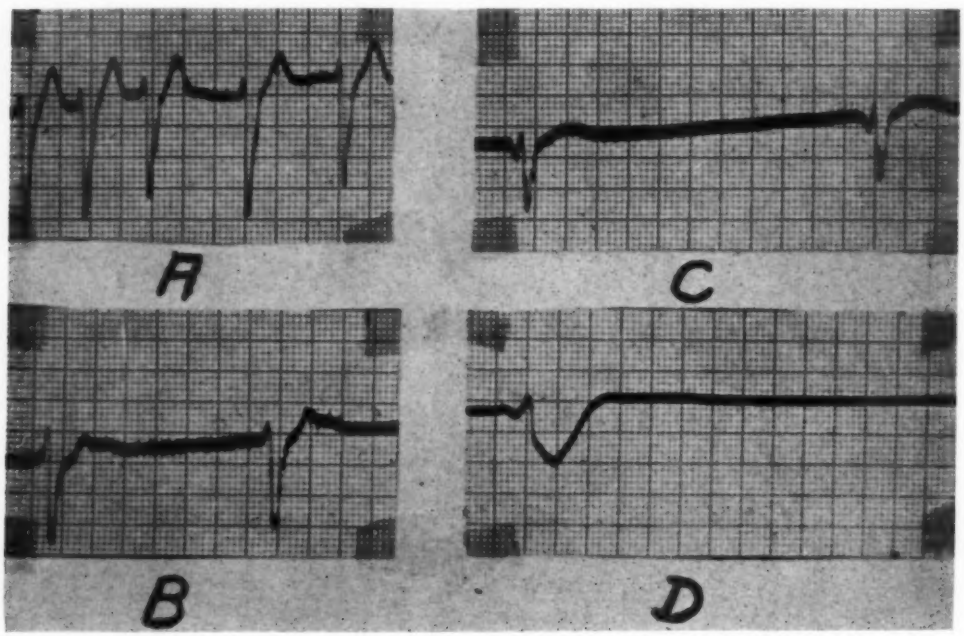

Fig. 4. (Case 4).—Cardiac standstill following quinidine (Lead CR_2). *A*, Initial tracing; *B*, 5 minutes after 0.65 Gm. given intravenously at once (convulsive seizure); *C*, 7 minutes after; *D*, 10 minutes after.

It is noteworthy that these instances of severe toxicity all occurred in patients with advanced heart disease and that in 2 cases the arrhythmia was presumably due to digitalis overdosage. In Case 2 the widening of the QRS complex should have been a warning to cease giving quinidine. In Case 4 which was the first one treated in this series, the fatality was probably attributable to the single large dose of 0.65 Gm.

It may be observed that in 1 patient with ventricular tachycardia due to digitalis toxicity intravenous quinidine proved life saving. This subject, who had hypertensive heart disease, had been receiving 0.2 mg. of digitoxin daily for several weeks and also an unknown amount "on the side." He was hospitalized

with ventricular tachycardia, rate 204 per minute, and was semicomatose, in shock, with the blood pressure unobtainable. After 0.13 Gm. of quinidine the rate began to slow and after 0.4 Gm. was 162 per minute. At this point the QRS complex began to widen and administration of quinidine was stopped when 0.6 Gm. had been given. Thirty minutes after the last dose a tonic convulsion occurred and with this sinus rhythm was restored.

In another patient with severe heart disease quinidine likewise was life saving. This subject, who had hypertensive heart disease and acute posterior wall infarction, had ventricular tachycardia of several hours' duration with a rate of 200 per minute; he was in profound shock and coma. Immediately after 0.13 Gm. of quinidine the ventricular tachycardia ceased but recurred in transient paroxysms at a rate of 150 per minute. An additional 0.13 Gm. restored a stable sinus rhythm with a rate of 58 per minute and only a few ventricular premature beats.

An important electrocardiographic change which occurred in 7 patients with auricular fibrillation and 5 with auricular flutter was an initial acceleration of the ventricular rate with the production of functional bundle branch block. As indicated by the cases of auricular flutter, the initial effect of quinidine was a slowing of the auricular circus movement with the result that a change occurred from a 4 to 1 ventricular response to a 2 to 1 response, or 2 to 1 flutter temporarily changed to a 1 to 1 response. With increase in the rate of the impulses passing through the conduction system, temporary functional impairment appeared with the development of bundle branch block. In 1 case quinidine slowed the auricular circus rate from 380 to 214 per minute with slowing of the ventricular rate, and in this subject functional bundle branch block which had been present with the initial rapid ventricular rate disappeared.

COMMENT

Intravenous quinidine exhibits therapeutic activity in cardiac arrhythmias identical with oral quinidine. The one significant pharmacological difference is in the speed of action. The effect of intravenous quinidine on the heart is almost immediate in minimal dosage, as indicated by termination of arrhythmias in certain cases, by slowing of circus movement in auricular flutter, and by the appearance of typical quinidine effects in the electrocardiogram, i.e., flattening of the T wave and prolongation of the Q-T interval. The action of oral quinidine is much slower in onset. Maximum blood levels following single large doses are attained after 2 to 4 hours, and the effect on the heart as studied by changes in the circus movement in cases of auricular fibrillation and flutter is similarly delayed.[4-7] Therapeutically effective levels cannot be attained with single doses, however large, and it is necessary for this purpose to administer oral doses of 0.4 to 0.6 Gm. every 2 hours for 5 doses.

The promptness of action of intravenous quinidine affords a means of appraising the efficacy of the drug in cardiac arrhythmias. Since disorders of rhythm are frequently transitory, it is at times difficult to know whether restoration to sinus rhythm following oral quinidine is due to the drug or is a spontaneous

occurrence. Experience gained in the present study provides a guide to the employment and limitations of oral quinidine. Stated briefly, quinidine is highly effective in acute arrhythmias and is of little or no avail in chronic disorders of rhythm. It is effective in the various common types of arrhythmias. It is most efficacious in subjects with no known organic heart disorder or in those who have only minor organic impairment. It is frequently effective in arrhythmias occurring in acute myocardial infarction. The drug is of no avail in subjects who have advanced heart disease with cardiac enlargement and decompensation and is hazardous in this group. It is likewise hazardous in arrhythmias due to digitalis toxicity. It is dangerous when disorders of conduction are present, i.e., bundle branch block and heart block. It should be kept in mind, however, that tachycardia itself may be responsible for the production of a functional bundle branch block, due to fatigue of the conduction system, which may disappear when regular sinus rhythm is restored.

The development of serious arrhythmias in 5 subjects, leading to death in 4, emphasizes the toxic potentialities of quinidine. Armbrust and Levine[9] similarly encountered 4 deaths produced by intravenous quinidine employed in 31 cases of ventricular tachycardia. These fatalities, as in those observed in the present study, all occurred in subjects with advanced organic heart disease who were in shock or had congestive heart failure. Ordinarily, administration of quinidine by the intravenous route appears neither desirable nor necessary. If used, the following precautions should be observed. Quinidine should be administered slowly in doses of 0.13 Gm. at intervals of 5 minutes or longer, with concurrent electrocardiographic observation employing a direct writing apparatus. In this manner if abnormalities such as bundle branch block, atrioventricular conduction disturbances, or new ectopic rhythms develop, further administration must be discontinued before severe toxicity supervenes. If the drug is effective, it will usually restore sinus rhythm with a small dose, i.e., less than 0.65 Gm.

It is to be emphasized that toxic arrhythmias produced by quinidine as found in the present study may occur also with oral quinidine. The frequency of potentially dangerous changes in rhythm with quinidine (notably, speeding up of the ventricular response in auricular fibrillation and flutter and impairment of the conduction system) dictates careful supervision when quinidine is given therapeutically. Although quinidine is frequently effective in ventricular arrhythmias,[9] it cannot be considered a drug of choice. Three of the 4 deaths in the present study occurred in subjects with ventricular tachycardia, and in another subject ventricular tachycardia was precipitated by quinidine. Procaine amide hydrochloride has recently been reported to be effective in abolishing ventricular arrhythmias,[10] and because of its safety by the oral and intravenous routes this drug appears preferable in ventricular ectopic rhythms. It may be recommended that the use of quinidine be confined to acute arrhythmias of supraventricular origin and that in ventricular tachycardia its use be reserved until other safer measures have been tried. It is to be emphasized that quinidine is of little avail in long-standing arrhythmias and is hazardous in subjects with advanced organic heart disease, particularly in the presence of congestive heart failure or digitalis intoxication.

SUMMARY AND CONCLUSIONS

Quinidine lactate was administered intravenously to 44 subjects with cardiac arrhythmias. The most significant factors determining its effectiveness in restoring regular sinus rhythm were found to be the acuteness of the arrhythmia and the absence of advanced organic heart disease. Conversion to normal rhythm occurred in 22 of 28 subjects in whom the arrhythmia was of brief duration, and in none of the 16 patients with chronic arrhythmias. The effectiveness of quinidine did not appear to bear any clear-cut relationship to the type of arrhythmia. There was no evidence in the cases studied that previous digitalization enhanced the therapeutic effect of quinidine.

Unless quinidine is employed judiciously and with adequate control, it is a hazardous drug. Quinidine is totally ineffective in subjects with congestive heart failure and is hazardous in this group due to the propensity to develop serious toxic arrhythmias. The drug is likewise dangerous in arrhythmias due to digitalis toxicity and in subjects in whom disorders of conduction are present, i.e., bundle branch block and heart block. In this series serious arrhythmias resulting from quinidine administration occurred in 5 cases leading to death in 4 subjects. Complete heart block and cardiac standstill developed in 3 of these patients, ventricular fibrillation and ventricular tachycardia in the other 2. All these subjects had advanced heart disease and in 2 cases the arrhythmia, for which quinidine was given, was presumably due to digitalis intoxication.

The pharmacological actions of intravenous quinidine are identical with those of oral quinidine. Careful supervision is necessary when quinidine is employed to terminate arrhythmias. It is to be emphasized that toxicity may occur equally with oral administration and that toxicity with oral quinidine has frequently gone unrecognized due to the extended period over which it is customarily given.

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THE USE OF PURIFIED VERATRUM VIRIDE ALKALOIDS IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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THE dissatisfaction which most physicians feel concerning the presently accepted treatment of essential hypertension is reflected in the current search for drugs which will lower the blood pressure over prolonged periods. As a result of this search, attention has again been directed to veratrum viride. Sporadic reports on the use of veratrum alkaloids for their hypotensive effects in both medical and obstetrical cases appeared during the early years of this century.[1-4] Interest waned, however, because of toxic symptoms, variability of drug lots, and relative impurity of the available preparations. Recently, enthusiastic reports have appeared in the obstetrical literature concerning the treatment of eclampsia with veratrum.[5,6]

In the past ten years relatively pure mixtures of veratrum alkaloids have been made available. These include Vertavis, Veratrite, Veratrine, Veriloid, Veratrone, and Anatensol. The pharmacologic properties of veratrum alkaloids have been thoroughly studied in animals by Krayer and Acheson.[7] Freis and associates[8] and Wilkins and associates[9] have extended these studies to human beings and have concluded that the veratrum alkaloids are not sympatholytic agents and that vasomotor reflexes are preserved. The cardiac output and blood flow to the extremities and vital organs were found to be normal during the hypotensive effect of the drug. They postulated that the primary action of these alkaloids in producing a hypotensive effect is mediated through the central nervous system. An undesirable side effect of the drug is stimulation of the vagus and emetic center. The dose which produces nausea and vomiting is only slightly greater than the dose necessary to lower the blood pressure.

These pharmacologic studies and preliminary clinical reports seemed to warrant controlled clinical evaluation, and a supply of Anatensol† was obtained. The drug was supplied in 0.5 mg. uncoated tablets in lots A and B. Lot A was aid to disintegrate in the stomach about thirty times faster than Lot B.

SELECTION OF CASES AND METHODS OF ADMINISTRATION AND FOLLOW-UP

The group treated with Anatensol consisted of twenty-five patients with essential hypertension between the ages of 28 and 60 years. All manifested

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resting blood pressures of 160/100 mm. Hg or more. Initial investigation included history and physical examination, teleroentgenogram of the chest, electrocardiogram, routine urinalysis, phenolsulfonphthalein excretion test, nonprotein nitrogen and Kahn tests. Blood counts, pyelograms, and exclusion tests for pheochromocytoma were performed when indicated. All blood pressure readings were taken from the left arm after the patients had rested for ten minutes in the supine position. The control period varied from two to six months, during which time patients visited the clinic at monthly intervals. After drug treatment was started, the patients were seen at weekly intervals by one of four physicians. The drug was administered in divided daily doses after meals and at bedtime, and frequently tincture of belladonna or Dramamine were given in an attempt to prevent or reduce nausea and vomiting. A gradually increasing dosage was employed, beginning with small amounts. Meticulous attention to dosage was observed in order to minimize the unpleasant side effects which may be encountered. Conventional measures for the care of hypertensive patients were instituted during the control period and were continued throughout the specific treatment phase of the study. These measures were used only as indicated and included mild sedation, limitation of activity, digitalis and diuretics, moderate salt restriction, social service consultation, and superficial psychotherapy.

RESULTS

Individual case summaries are included in the table. An average sustained drop of 20 mm. Hg systolic and 10 mm. Hg diastolic pressure was considered significant. The group can be divided into three general categories:

1. In the first group of five patients (No. 1 through 5) a significant drop in blood pressure was produced. Daily dose necessary for this beneficial effect varied between 3 and 8 mg. Two of the five patients did not experience toxic symptoms, and the other three tolerated effective doses with only slight nausea. Since none of these patients had been experiencing symptoms definitely related to hypertension prior to treatment, symptomatic response could not be judged. No changes in electrocardiograms or heart size were observed in this group.

2. The second group of twelve patients (No. 6 through 17) tolerated an amount of the drug ordinarily expected to produce some hypotensive effect. This amount varied between 2 and 6 mg. each day. In each case no hypotensive effect was noted, and further attempts to increase the daily dose of Anatensol were unsuccessful because of the appearance of nausea and vomiting.

3. In the third group of eight patients (No. 18 through 25) adequate therapeutic trial was precluded by the immediate or early onset of distressing gastrointestinal side effects. Actually, the last six of this group failed to tolerate even as little as 0.5 to 1.0 mg. of the drug by mouth per day, and the other two were able to tolerate no more than 1 to 2 mg. daily, an insufficient amount to produce any hypotensive effect in our experience.

It should be noted that there was no significant difference in the nausea and vomiting produced by lots A and B of Anatensol. This would seem to mean that local gastric irritation due to a too rapid disintegration of the tablet does not play an important part in the nausea. Atropine, although it abolished the

TABLE I. HYPERTENSIVE PATIENTS

PATIENT	SEX	AGE (YEARS)	CONTROL PERIOD					MAXIMUM DAILY ORAL DOSE (MG.)
			DURATION OF HYPERTENSION (YEARS)	DURATION (MONTHS)	BLOOD PRESSURE			
					LOW	HIGH	MEAN	
1. A. D.	M	47	Unknown	2	170/120	200/135	180/125	6
2. L. E.	F	39	2	2	290/175	300/190	295/185	6
3. V. G.	F	44	10	6 wk.	235/125	235/135	345/130	8
4. C. P.	M	54	12	1 yr.	240/130	300/170	245/150	9
5. C. McC.	F	45	11	4	200/120	230/150	220/130	3
6. V. G.	F	50	10	1	230/140	230/160	230/150	2
7. J. K.	M	37	4	2	240/130	260/160	250/150	3–4
8. P. S.	M	52	11	3	180/120	210/130	200/120	4–6
9. M. S.	F	46	6	2	170/100	180/110	170/105	3–4
10. E. M.	F	51	2	2	190/105	220/110	200/110	3
11. P. P.	M	51	10	8	210/110	240/140	220/120	3
12. W. M.	M	50	9	2	190/110	210/130	200/120	6–8
13. J. M.	M	41	3	1	155/120	160/120	158/120	5–6
14. L. C.	F	51	10	2	190/130	220/130	200/125	4–6
15. E. W.	F	40	2	5	230/140	260/170	245/155	3
16. S. P.	M	43	5	7	175/125	220/140	200/135	3–4
17. L. C.	F	28	1	5	215/125	170/100	190/110	3–5.5
18. A. H.	F	49	6	3	170/100	220/130	190/110	1–3
19. H. R.	F	37	8	2	170/90	190/110	180/105	1
20. A. F.	F	49	15	2	140/110	185/130	165/115	1
21. R. W.	M	50	13	3.5	190/110	230/140	210/125	1
22. A. S.	F	41	10	7	220/110	270/135	240/130	1
23. L. M.	F	45	2	2	210/120	280/150	235/140	1
24. N. H.	F	60	1	1 yr.	170/95	240/130	190/105	2
25. M. L.	F	38	6	5	160/95	200/130	180/120	1

bradycardia, had little to offer as far as nausea was concerned, and Dramamine, in a limited trial, did not seem to offer much more.

A more detailed discussion of the first group is necessary. Patient 1 (A. D.) experienced one of the most satisfactory responses of our group. From an average blood pressure of 180/125 during the control period, there was a fall to 115/85

TREATED WITH ANATENSOL

ANATENSOL ADMINISTRATION		RESULTS OF TREATMENT			
PERIOD OF TREATMENT (MONTHS)	TOXIC EFFECTS	BLOOD PRESSURE			GENERAL ESTIMATE OF EFFECT ON BLOOD PRESSURE
		LOW	HIGH	MEAN	
5	None	115/85	170/120	145/115	Definite reduction
3	None	260/150	275/160	270/160	Definite reduction; died 2 mo. later, cerebral accident
6	Some nausea early in course	170/100	250/140	215/120	Definite reduction
4	Slight nausea	175/135	300/160	210/145	Reduction (died of uremia)
3	Some nausea and vomiting early	220/130	235/130	200/120	Slight reduction
2	None	230/140	230/160	230/150	No effect
3	3 mg. tolerated; 4 mg. produced severe nausea and vomiting	230/120	260/160	245/145	No effect; died 2 mo. later of malignant hypertension
4	4 mg. tolerated; 6 mg. produced severe nausea and vomiting	180/110	210/140	195/120	No effect
5	3 mg. tolerated; 4 mg. produced severe nausea and vomiting	140/90	175/120	160/105	No definite effect
5	Slight nausea	180/100	210/120	190/110	No effect
2	Nausea	210/120	260/150	215/130	No effect
7	6 mg. tolerated; 8 mg. produced severe nausea and vomiting	170/110	210/140	190/120	No effect
3	5 mg. tolerated; 6 mg. produced severe nausea and vomiting	140/98	190/140	155/120	No effect
3	4 mg. tolerated; 6 mg. produced nausea and vomiting	210/110	240/130	220/120	No effect
3	Nausea and vomiting on 3 mg.; tolerated 2 mg.	220/140	250/160	235/150	No effect
2.5	3 mg. tolerated; 4 mg. produced nausea and vomiting	230/150	250/160	235/150	No effect
4	3 mg. tolerated; 5.5 mg. produced nausea and vomiting	210/130	175/105	200/115	No effect
2	1 mg., weakness; 2 mg. nausea; 3 mg., severe nausea, salivation	170/100	215/130	185/110	No effect
2	1 mg. tolerated; nausea and vomiting on higher dose	170/105	180/120	175/110	No effect
1 wk.	1 mg. produced nausea and vomiting	No change			Drug toxic
1 wk.	1 mg. produced nausea and vomiting	No change			Drug toxic
2 wk.	1 mg. produced nausea and vomiting	No change			Drug toxic
2 days	1 mg. produced nausea and vomiting, diarrhea, precordial pain	No change			Drug toxic
3 days	2 mg. produced severe nausea and vomiting	No change			Drug toxic
2 wk.	1 mg. produced nausea and vomiting	No change			Drug toxic

on 4 mg. of Anatensol daily. However, maintenance on this dose was attended by a gradual rise to 170/110 after three months, and further increase in Anatensol to 7.5 mg. daily resulted in nausea and vomiting but no change in pressure except for a rise of the diastolic pressure to 140. Reduction to 6 mg. daily, which did not cause nausea, did not affect the blood pressure.

It would seem, then, that in some patients tachyphylaxis is noted, and further increase in the dose of the alkaloid serves only to bring on, or intensify, toxic symptoms.

Patient 3 (V. G.), on the other hand, had a sustained fall in both systolic and diastolic pressures which was maintained for four months with no increase in dose. A change to the same dose of a placebo tablet resulted in an immediate significant rise, particularly of the diastolic pressure. It would seem then that the rate of development of tachyphylaxis is variable. It is possible that some of our failures to maintain a sustained drop, as in patients 13 (J. M.) and 9 (M. S.), were due to early tachyphylaxis.

One patient (No. 4, C. P.) was in the malignant phase of essential hypertenr sion, and it should be noted that although he died of uremia four months aftebeginning the drug, the rapid downhill course of his illness seemed to be slowed. No new hemorrhages or exudates appeared in the eye grounds during treatment. An autopsy done on this patient with special attention being paid to possible toxic effects of Anatensol failed to reveal any pathologic changes which could be attributed to the drug.

DISCUSSION

The literature contains reports of approximately 150 hypertensive patients treated with alkaloids of veratrum viride during recent years.[10-14] There can be little doubt that the drug has been strikingly effective in reversing an unfavorable clinical course in occasional cases of hypertensive encephalopathy or malignant hypertension with or without congestive heart failure. However, the great majority of patients reported were not in any hypertensive crisis, and for the most part information concerning symptoms secondary to hypertension is unavailable. Previous clinical studies and the present one must be considered short-term attempts to alter the course of a disease which characteristically persists for many years and in which elevation of blood pressure is only one of many manifestations.

Hite[10] reported a series of thirty patients treated with a biologically standardized preparation of the powdered whole plant of veratrum viride. The average of at least three separate blood pressure readings taken at intervals of a few weeks was used as a control. The average fall in systolic pressure was 26 mm. Hg and in diastolic 14 mm. Hg. Sixty per cent demonstrated a systolic fall of more than 25 mm. Hg and a diastolic fall of more than 20 mm. Hg. He reported failure in four cases, or 13.3 per cent, and these patients manifested advanced renal disease. Toxic reactions developed in only two of the thirty patients.

Freis and Stanton[11] have reported a series of forty patients treated with Vertavis over a period of several weeks to thirteen months. An effective blood pressure drop was described as 20 mm. Hg systolic and 15 mm. Hg diastolic. Five out of six hospital patients manifested satisfactory responses, while thirty out of thirty-four outpatients showed significant blood pressure drops. The outpatient results were seldom striking compared to the hospital group. Seventy-nine per cent showed subjective improvement, and, occasionally, reversal toward normal of abnormal eye grounds, electrocardiograms, and cardiac size as shown

by chest roentgenogram was noted. Toxic manifestations occurred but were not a serious problem. The authors concluded that Vertavis was useful in the treatment of certain cases of hypertension and that the long-term effects of this drug were significant but not dramatic.

Successful use of Veriloid, a relatively new extract of veratrum viride, has been described in ten hospital patients and twenty-five ambulatory patients by Wilkins, Stanton, and Freis.[12] Acute experiments performed in the hospital revealed an average fall of 43 mm. Hg systolic and 38 mm. Hg diastolic pressure after an unspecified oral dose. Four patients exhibited nausea or vomiting. Ambulatory patients received from 6 to 11 mg. of Veriloid each day in four divided doses. Nine were followed from twelve to twenty weeks and exhibited an average blood pressure fall of 33 mm. Hg systolic and 25 mm. Hg diastolic. Eleven patients treated for six to twelve weeks demonstrated average falls of 37 mm. Hg systolic and 24 mm. Hg diastolic. Five patients treated for two to four weeks showed average falls of 36 mm. Hg systolic and 17 mm. Hg diastolic. Throughout the study meticulous attention to dosage was necessary to minimize nausea and vomiting which is so prone to occur with any veratrum derivative. The control periods consisted of forty-eight hours' observation in the hospitalized patients and three blood pressure readings at unspecified intervals in the ambulatory patients. These authors concluded that Veriloid was an active hypotensive agent, and that nausea and vomiting were experienced somewhat less often than with other veratrum preparations.

Coe, Best, and Kinsman[14] have reported unsatisfactory results in the treatment of twenty-five ambulatory hypertensive patients with Vertavis. A majority of their patients failed to demonstrate a satisfactory drop in blood pressure. Sixty-four per cent noted symptomatic improvement while on the drug, but 60 per cent also noted improvement when placebo was substituted for Vertavis. Toxic symptoms from the drug were noted in 64 per cent.

McNair, Griffith, and Elek[13] have noted similar results in a series of twenty-two patients treated with Vertavis over periods varying from two to five months. Toxic manifestations did not prove to be of unusual magnitude in their group; however, statistical analysis of the results failed to show any significant depression of blood pressure. Their average patient tolerated a higher daily dose than the patients in the group treated by Freis and Stanton.

Our experience with Anatensol in this series of twenty-five patients offers distinct contrast to the first three groups of patients just cited. However, our results are in agreement with those of McNair, Griffith, and Elek and Coe, Best, and Kinsman. The incidence of nausea and vomiting was high in spite of adherence to recommended cautious dosage schedules, and the number of patients exhibiting significant reductions in blood pressure was low. In no case were the toxic symptoms of a serious nature, and vagal collapse, as has been occasionally noted, did not occur. It was originally hoped from animal experiments that this highly purified compound would exhibit a high therapeutic index in hypertensive patients, but our experience has not confirmed this. We know of no way to predict which patients will exhibit intolerance to the drug and which patients will maintain a significant blood pressure fall. It has been suggested that the

gastrointestinal side effects may constitute an integral part of the reflex pattern initiated by veratrum and that the emetic and hypotensive properties are inseparable.[7]

SUMMARY

Twenty-five patients were treated with Anatensol, a purified extract containing two alkaloids of veratrum viride. In only five patients was a significant, sustained hypotensive response noted. In all of the others the appearance of distressing nausea and vomiting in spite of meticulous attention to dosage prevented adequate trial.

Until it has been shown that the relatively noxious alkaloids of veratrum viride effectively alter the long-term course of hypertensive vascular disease and do not merely lower the blood pressure temporarily in an occasional patient, we decry the widespread recommendation and use of these products.

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AN EVALUATION OF METHODS OF DICUMAROL ADMINISTRATION

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DICUMAROL dosage has been a difficult problem ever since the drug was introduced into clinical medicine. The effects of the anticoagulant are delayed after its administration, and their intensity and duration are erratic. The recent development of a method for determining the concentration of Dicumarol in plasma and other biological materials has made it possible to study the absorption, excretion, rate of transformation, and physiologic distribution of the drug.[1,2,3] This newer knowledge has permitted the more adequate investigation of the rationale behind the various regimens of Dicumarol administration which have been in clinical use.

The ideal method of administration of most drugs achieves and maintains a concentration in the body which has been found to be safe and effective. In the case of Dicumarol, experience has taught that one can rarely predict a given daily dose which will be effective and free of the hazard of hemorrhage when administered over an extended period of time. To control Dicumarol therapy properly the influence of the drug upon the prothrombin time must be carefully followed.

Physiologic studies reported elsewhere[2,3] have revealed the following facts which have been helpful in the establishment of a rational schema for Dicumarol dosage:

1. The drug may be absorbed slowly from the gastrointestinal tract. In some instances peak plasma concentration following single oral doses may not be achieved for more than twenty-four hours.
2. Absorption may be incomplete. From zero to more than 40 per cent of a single oral dose may be eliminated in the stool.
3. The drug is not excreted in the urine.
4. The drug is metabolized in the body at a slow rate, and this varies considerably with the individual and with the dose. Larger doses are transformed at a slower rate. Plasma levels may fall as slowly as 15 per cent per day or more rapidly than 50 per cent. Subjects in a stable metabolic state tend to degrade the drug in a more or less consistent manner.
5. The drug is widely distributed in most tissues. Repeating a dose while there is still Dicumarol in the body results in an increment of a plasma level greater than the peak level achieved by that dose initially.
6. There is a threshold concentration of Dicumarol in the plasma which must be achieved before any prothrombin response can be detected. This level varies considerably in different subjects.
7. There is considerable individual variation in the "sensitivity" of the prothrombin mechanism to a given plasma level of Dicumarol. A level which results in dangerously high prothrombin time in one subject may fail to induce a prothrombin response in another.

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8. The pattern of the prothrombin response is roughly parallel to, and one to two days behind, the plasma Dicumarol concentration. In some sensitive individuals the prothrombin time may remain elevated long after the Dicumarol has disappeared from the plasma.

9. Water-soluble preparations of vitamin K are effective in reducing the prothrombin time but do not influence the rate at which Dicumarol disappears from the plasma. Repeated large doses of vitamin K are necessary to reduce the prothrombin time if the concentration of Dicumarol in the plasma is high.

SCHEMATA OF DICUMAROL ADMINISTRATION

Empirical Method.—Shortly after Dicumarol was first introduced, it became apparent that the drug could not be given empirically and that the dose should be individualized. Statements emphasizing this are to be found in the earliest publications on the subject.[4] It is most unfortunate, as it is amazing, that from time to time, cases are revealed in which Dicumarol has been administered without control by adequate estimation of prothrombin time. Such therapy is destined to result either in inadequate response on one hand or bleeding on the other.

Maintenance Dose Method.—This widely attempted method aims at achieving and maintaining a "therapeutic range" of reduced prothrombin activity. It requires the administration daily, or almost daily, of a maintenance dose of the drug. Usually a relatively larger dose is given initially (300 mg. the first day, 200 mg. the second day), and following this, a small dose is given daily or on staggered days in an attempt to obtain and maintain a constant elevation of the prothrombin time within a safe range. The estimation of prothrombin time is made daily, and the magnitude of the dose of Dicumarol for that day is judged accordingly.

This method takes into account only the momentary prothrombin time, but it fails to take into consideration whether the prothrombin time is rising or falling. Since peak Dicumarol levels may not be reached for twenty-four hours after an oral dose and since peak prothrombin responses may follow Dicumarol levels by forty-eight hours, the "maintenance dose" method may result in the administration of additional Dicumarol when the prothrombin time is already destined to become high. In addition, daily doses may accumulate to high levels insidiously, especially in persons who dispose of the drug slowly, resulting in delayed and dangerously high prothrombin responses. On the other hand, small repeated doses may be transformed at a relatively rapid rate, and many days may pass before it is realized that the daily dose being given is inadequate. Where variability in absorption occurs, the effect of repeated doses becomes wholly unpredictable. The use of even smaller doses repeated more frequently than once each day makes prediction of response even more difficult. In general, frequent administration of a drug may be essential only if the agent is rapidly excreted or transformed by the body. Drugs which disappear from the plasma as slowly as Dicumarol can be controlled better by relatively infrequent administration of doses, the magnitude of the doses being determined by the needs of the patient.

Intermittent Dosage Schedule.—Because of the difficulties encountered in predicting the trend of the prothrombin time during daily maintenance dosage,

we prefer a method of intermittent dosage. By this method a large single* dose of Dicumarol is given initially so that an adequate initial response is obtained. The prothrombin time is then followed with no further immediate dosage of Dicumarol. Serial estimations of the prothrombin time are made, and after the peak prothrombin response is passed and the prothrombin time is falling toward normal, another single effective dose is administered. Following this dose, the peak prothrombin response is again observed and again a single effective dose is given. This cycle is continued for the duration of the therapy. By this method it is possible at any moment to decide to which dose the prothrombin time is responding; a downward trend, once observed, will continue to decline until the drug is again administered. There is no problem of accumulation, and failure of absorption can be recognized promptly. Subjects who transform Dicumarol rapidly may require doses as frequently as every two or three days, while "slow transformers" may require doses only at intervals of ten days or more.

There is no empirical rule for estimating the size of the initial dose. Several factors must be evaluated. One must consider:

1. *Weight of the patients*: Doses should be calculated on the basis of milligrams per kilogram, although there is room for error particularly in obese patients. Nevertheless, this has been found the most reliable method for determining dosage.

2. *Age of patient*: Older persons are apt to be Dicumarol sensitive.

3. *Nutritional state*: Poor recent nutrition frequently increases sensitivity to Dicumarol. Salicylate medication may enhance the response to Dicumarol and should be avoided when Dicumarol is given.

4. *Severe anemia*: Patients with low hemoglobin values are usually Dicumarol sensitive.

5. *Liver disease*: Only under exceptional circumstances should patients with Laennec's type of cirrhosis of the liver be given Dicumarol. Congestive hepatomegaly is not a contraindication. Obstructive biliary disease may result in Dicumarol sensitivity because of the concomitant vitamin K deficiency or hepatocellular dysfunction.

6. *Initial prothrombin time*: Subjects exhibiting hyperprothrombinemia† generally require larger initial doses of Dicumarol than persons with normal prothrombin time. The drug should be given most cautiously if the prothrombin time is initially prolonged. If there is pre-existing marked hypoprothrombinemia, the drug should be withheld unless the therapy is imperative.

7. *Urgency of therapy*: As is often true of other therapeutic measures, a calculated risk is frequently necessary. In treating a patient with recurring pulmonary emboli, each of which may be life threatening, one should err on the side of overdosing rather than underdosing. On the other hand, it is preferable to risk underdosing in initiating medication to patients with relatively mild thrombotic disorders for whom long-range therapy is contemplated. It should be realized that after the acute thromboembolic process has subsided, the therapy should be continued at a prophylactic dosage level which is significantly less than that required for therapeutic anticoagulant effect.

8. *Past history*: Patients who have had or are suspected of having ulcerative gastrointestinal or other bleeding lesions should be evaluated carefully and treated most cautiously.

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*When therapy is urgent, a safe portion of the initial dose is given immediately, and the remainder of the initial dose given a few hours later after the control prothrombin time is reported and the magnitude of the dose established. Subjects with hyperprothrombinemia or with mild but significant hypoprothrombinemia can be detected by determining the control prothrombin time of saline-diluted (12.5 per cent) plasma.

†See preceding footnote.

By taking all of the above factors into consideration, one may arrive at an initial dose of as little as 200 mg. or as much as 1,000 or 1,100 mg. A peak prothrombin response of two to two and one-half times the normal control value in the whole plasma and about three times the normal control in the diluted (12.5 per cent) plasma prothrombin time is considered desirable.*

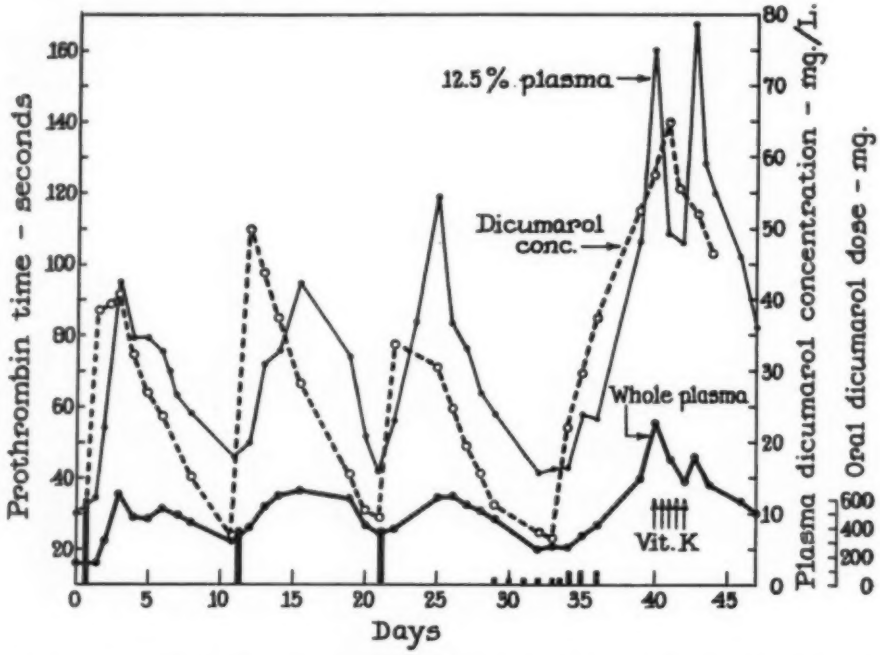

Fig. 1.—Dicumarol dosage, Dicumarol plasma concentration, and prothrombin response of a patient who was given Dicumarol both intermittently and in continuous daily dosage. Lower solid line: whole plasma prothrombin time; upper solid line: saline-diluted (12.5 per cent) plasma prothrombin time; broken line: Dicumarol plasma concentration; solid bars: oral administration of milligrams of Dicumarol.

Subsequent doses are judged by the response to the previous dose. Each dose is given when the prothrombin time has declined to about one-half the time to the control value (about 25 seconds in whole plasma, 65 seconds in diluted [12.5 per cent] plasma). If the initial dose results in the desired response, a repeat dose one-half its size may be expected to cause again the desired prothrombin response. If the initial response is greater or less than desired, the subsequent dose is altered accordingly.

Some clinics have employed a "rule of thumb" procedure which, in practice, frequently proves to be a method of intermittent dosage. The Mayo workers, for example, suggested a dose of 200 mg. on each day that the prothrombin activity is reported to be greater than 30 "per cent of normal"† and none if

*With thromboplastin (Chilcott) or the newer preparation of Simplastin, this is equivalent to about 35 seconds in the whole plasma and 100 to 110 seconds in the diluted (12.5 per cent) plasma prothrombin time.

†The authors prefer to record prothrombin activity in terms of seconds of prothrombin time, rather than "per cent." The reasons for this preference have been discussed elsewhere.[2,5,6]

prothrombin activity is reduced to less than that figure. In this manner the confusion of small repeated doses is frequently eliminated, and one finds that most patients require 200 mg. about every two to four days. However, it is more logical to avoid giving a fixed dose for all subjects, but rather to individualize the size and frequence of dosage according to the needs of the patient and in consideration of the factors discussed above.

The following case is presented to illustrate the control afforded by the intermittent dosage method, and some of the problems which arise from administering daily doses of Dicumarol (Fig. 1).

The patient was a 46-year-old man who was relatively insensitive to Dicumarol (adequate prothrombin response required plasma Dicumarol levels of about 30 to 40 mg. per liter) and who transformed the drug slowly (about 16 per cent per day). An initial dose of 600 mg., followed by two doses of 400 mg. each at ten-day intervals, resulted in the desired prothrombin response over a period of one month. For purposes of comparison, continuous daily doses were then begun. Fifty mg. of Dicumarol per day were given for five days, but proved to be insufficient to cause a prothrombin response. On the sixth day two 50 mg. doses were given, and thereafter the daily dose was increased to 100 mg. The prothrombin time gradually rose to the desired level on the sixth day, and the drug was discontinued. On the seventh day the prothrombin time rose still further, and five doses of water-soluble vitamin K had to be given in the next two days to reduce the prothrombin time to safer levels. Discontinuing the vitamin K resulted in a new increase of prothrombin time in spite of the fact that no Dicumarol had been given for four days. Determination of the concentration of Dicumarol in the plasma indicated a marked accumulation of the drug in the plasma during the few days of 100 mg. per day. Only by the eighth day was this fact reflected in the resultant excessive prothrombin time.

SUMMARY

The physiological disposition of Dicumarol by the body is reviewed and its relationship to methods of Dicumarol dosage is discussed.

An illustrative case in which Dicumarol was given by both the continuous (daily) and the intermittent dosage methods is presented. The case illustrates: (1) the relationship of prothrombin response to plasma Dicumarol concentration; (2) the difficulty of recognizing promptly when a given daily dose of Dicumarol is inadequate; (3) the danger of undetected accumulation of daily doses to excessively high plasma Dicumarol concentrations; (4) the importance of knowing not only what the prothrombin time is at the moment, but also the direction in which it is changing; and (5) the better control of prothrombin response afforded by the intermittent dosage method.

CONCLUSION

Study of the disposition of Dicumarol by the body and its relation to prothrombin response indicates that the method of relatively large, infrequent, intermittent dosage is preferable to that of daily "maintenance" doses.

The technical assistance of Mr. Robert White is acknowledged. The thromboplastin used was supplied by the Chilcott Laboratories Division of The Maltine Company, Morris Plains, N. J. A rabbit-lung thromboplastin was employed. The present study was made before the availability of Simplastin (AM. HEART J. 40:766, 1950).

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Clinical Reports

PULMONARY STENOSIS WITH SURVIVAL TO THE AGE OF 78 YEARS

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PULMONARY stenosis with an intact septum was formerly considered a rare congenital heart lesion. In Abbott's Atlas[1] there were only nine cases among a thousand congenital hearts. However, cardiac catheterization studies seem to indicate that uncomplicated pulmonic stenosis may be one of the more common types of congenital heart disease.[2,3,4] In a recent review by Greene and associates,[4] sixty-eight cases of pulmonary stenosis with an intact septum were reviewed. In this series there were three patients who lived to the age of 70 years. Two of these died of heart failure, and one died of pulmonary and intestinal tuberculosis. This case is recorded since it is unusual for a person with this type of lesion to reach the age of 78 years.

CASE REPORT

History.—The patient (C. C.) was a white man, 78 years old at the time of admission to the hospital in July, 1948. His presenting complaints at that time were dyspnea, swelling of the abdomen and ankles, and weakness.

The patient, in 1898, had had a bout of rheumatic fever and was discharged after six months in the Armed Services because of rheumatic heart disease. The physical examination, while the patient was in the Army, described a very harsh systolic murmur over the left chest, the intensity of which was more marked over the second and third interspaces to the left of the sternum. A record of a physical examination in September, 1921, contained a note, for the first time, that the rhythm was totally irregular. After his discharge from the Army, the patient apparently did very well and worked in a machinery plant until 1943, at which time he had to discontinue work because of dyspnea on exertion. In 1945, he became orthopneic and developed swelling of the ankles and abdomen, and for a year prior to admission to the hospital, he had been confined to bed because of dyspnea, anasarca, and weakness. For the last two years of his life, the patient was an invalid. There was no history of cyanosis except during the last two years.

Physical Examination.—Physical examination revealed an elderly, dyspneic, orthopneic, pale white man who displayed marked distention of the veins of the neck in the upright position. Examination of the chest revealed signs of fluid at both pleural bases. The apical impulse was palpable in the sixth interspace in the left anterior axillary line. There was a systolic thrill palpable over the second left interspace. There was a harsh, Grade 4 systolic murmur heard over the

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second left interspace, which was transmitted toward the left clavicle and to the apex. The murmur was heard fairly well above the left clavicle. Along the left border of the sternum, there was a diastolic click. At the apex there was a systolic murmur and a short mid-diastolic murmur. The rhythm was totally irregular, and there was a pulse deficit of 16 per minute; the apical rate was 60 per minute. The blood pressure was 124/84 mm. Hg. Examination of the abdomen revealed ascites and, after repeated abdominal paracenteses, the liver could be felt three fingerbreadths below the right costal margin. There was edema of the scrotum and both lower extremities. Over both arms and lower extremities there were many purpuric areas of varying size. There was no clubbing of the fingers.

Laboratory Examination.—The urine revealed a specific gravity of 1.010, and there were occasional hyaline casts. The red blood cell count was 2,400,000 with 6 Gm. of hemoglobin. The hematocrit was 26 volumes per cent. There was free hydrochloric acid in the stomach. Total serum protein was 5.9 Gm. with 2.3 Gm. of albumin and 2.7 Gm. of globulin. Blood platelet count, prothrombin time, clotting time, and clot retraction time were all within normal limits. The blood Kahn was negative. Several stool specimens were negative for blood.

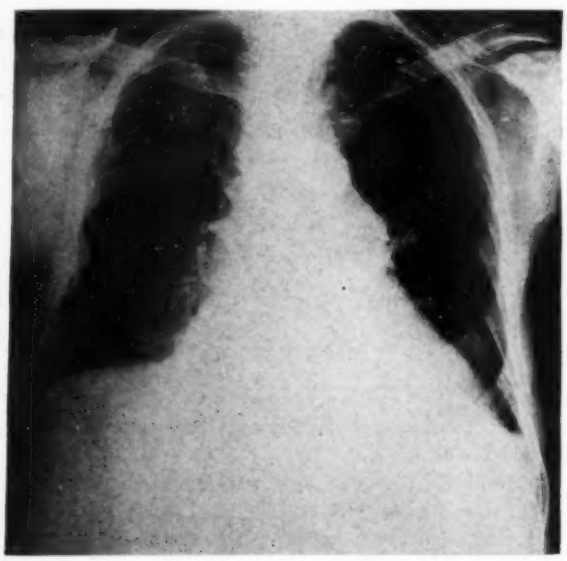

Fig. 1.—Roentgenogram of the chest revealing a moderately enlarged heart shadow with pulmonary artery.

X-ray examination of the chest revealed a moderately enlarged cardiac shadow with a prominent pulmonary artery (Fig. 1).

Fluoroscopic examination of the chest revealed marked dilatation of the pulmonary artery. There was no enlargement of the left auricle. In the right anterior oblique view, enlargement of the right ventricle was found. In the left anterior oblique position, the right ventricle again appeared prominent, and there was also questionable enlargement of the left ventricular component. Another fluoroscopic examination revealed enlargement of the right auricle, and during one examination some calcification was noted in the heart silhouette which could not be identified.

The electrocardiogram showed auricular fibrillation with a ventricular rate of 75 (Fig. 2).

The clinical diagnosis at this time (September, 1948) was mitral stenosis with an interauricular septal defect. The patient was placed on a low-sodium, neutral ash diet. The maintenance dosage of digitoxin, 0.1 mg, was continued. In addition, the following medications were administered: three blood transfusions, Brewer's yeast tablets (9 tablets daily), and vitamin B complex (2 capsules daily). Mercuhydrin was injected in a dosage of 1 c.c. at three-day intervals. The patient

was discharged on Sept. 14, 1948. He was readmitted to the hospital two weeks later with an interval history suggestive of multiple pulmonary infarctions. His course was rapidly downhill, and he died Sept. 30, 1948, thirty-six hours after admission.

Autopsy.—The essential findings at autopsy were in the heart and liver. Inspection of the heart revealed the contour to be enlarged. The heart weighed 650 grams. The right auricle and the pulmonary artery were unusually prominent. The right auricle contained a gray, firmly attached thrombus near the auricular appendage and another small thrombus on the posterior wall. The musculature of the right ventricle was considerably thickened and measured 8 mm. in thickness. The tricuspid valve showed a fissurelike lesion running perpendicular to the free edge of the valve and located on the left anterior cusp. The chordae tendineae in the neighboring portion of the cusp were thickened, fused, and shortened (Fig. 3). The pulmonic valve was bicuspid.

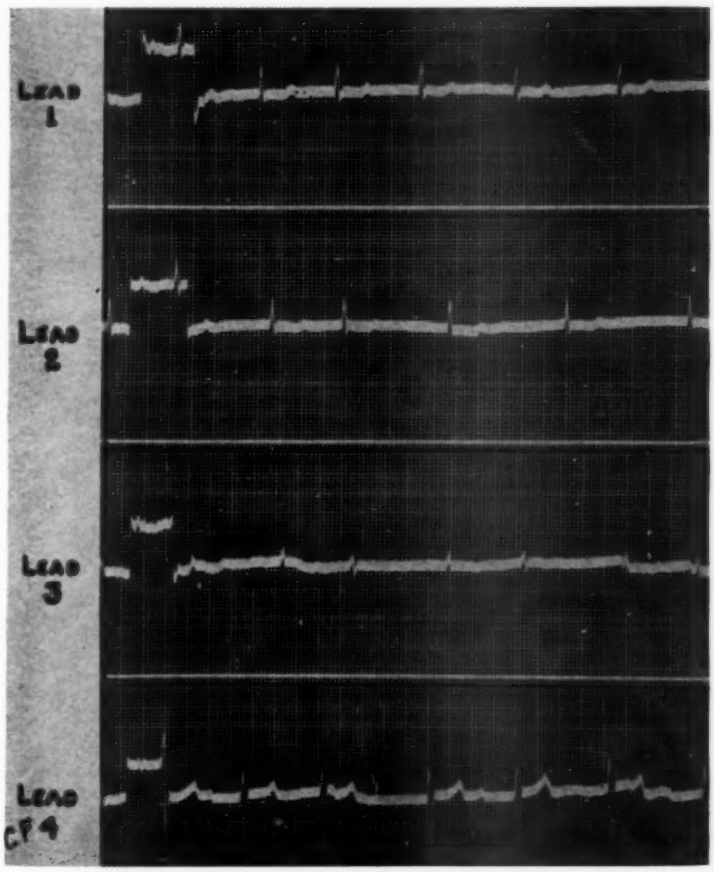

Fig. 2.—Electrocardiogram showing auricular fibrillation with digitalis effect.

and the cusps were markedly thickened. The commissure, which was located at the upper end of the interventricular septum, was markedly thickened and fused. There was a considerable amount of calcification at this commissure and in the basal portions of the two cusps (Fig. 4). The pulmonic orifice at the free edge of the cusp measured about 1 cm. in circumference. The valve formed a funnellike structure with the narrowest portion of the orifice at the free edge (Fig. 5). There was a marked poststenotic dilatation of the pulmonary artery, which measured 13 cm. in circumference at its widest point. The pulmonary artery exhibited a few focal atheroma-

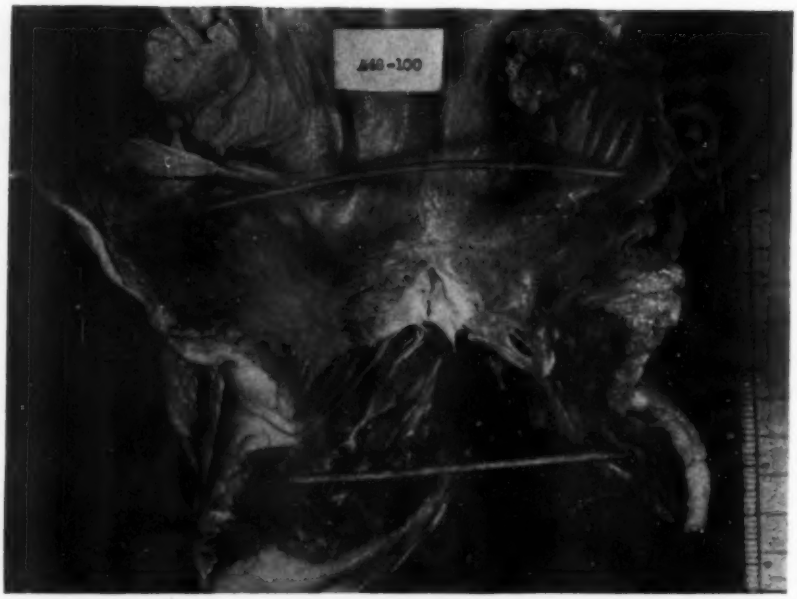

Fig. 3.—Showing fissurelike lesion of the tricuspid valve, shortening and thickening of chordae tendineae, and hypertrophy of the right ventricle.

Fig. 4.—Showing the bicuspid pulmonary valve (opened) with thickening and fusion at the commissure. The poststenotic dilatation of the pulmonary artery is clearly shown.

tous plaques beneath the intima. The mitral valve orifice measured 9 cm. in circumference. There was a fissurelike lesion on the anterior leaflet, presenting chiefly on the auricular surface. This was very similar in appearance to the lesion noted on the tricuspid valve. Small amounts of calcification were noted in the dense fibrous tissue forming the edges of the fissure. The chordae tendineae were thickened, fused, and shortened, and in some places the edge of the valve reached to the papillary muscle. The posterior leaflet of the mitral valve exhibited no significant abnormalties (Fig. 6). The aortic valve cusps were much calcified with the calcification extending from their bases almost to their free edges. There was fusion of the commissures for a distance up to 4 to 5 mm. The lunulae were also thickened. There was no significant shortening of the valve cusps. The orifice measured 7 cm. in circumference. The membranous portion of the

Fig. 5.—Showing the funnellike opening of the pulmonary valve orifice with dilatation of the pulmonary artery.

interventricular septum just below the aortic valve appeared in the form of a cuplike depression from the left ventricular aspect. The root of the aorta and the aortic valve lay definitely to the right of the interventricular septum, almost 2 cm. more to the right than the usual location (Fig. 7). The coronary arteries exhibited extensive calcification with some points of occlusion of the anterior descending branch of the left coronary artery. However, there were no points of complete closure.

The liver was moderately enlarged, weighing 1,900 grams. The serosal surface was nodular and irregular with nodules protruding above the general surface. These measured from 5 mm. to 1 cm. in diameter. The general color of the liver was brownish red. On cut section, there was increased resistance to the knife, and nodules of hepatic tissue, separated from one another by fibrous streaks, were seen throughout the liver substance. Some evidence of chronic passive congestion was noted in the hepatic parenchyma. Sections through the liver showed an advanced cirrhosis with some congestion of the hepatic parenchyma. Anasarca was also present at the time of autopsy. Microscopic examination of the heart showed only slight focal fibrosis of the myocardium. No Aschoff bodies were found.

DISCUSSION

The clinical impression shortly after the patient was admitted to the hospital was that the patient had Lutembacher's syndrome. The history of rheumatic fever in 1898, the physical findings of mitral stenosis, a harsh systolic murmur over the second left interspace, the dilatation of the pulmonary artery, and the absence of left ventricular enlargement seemed to fulfill the criteria for the diagnosis of a Lutembacher's syndrome. In retrospect, the possibility of pulmonary stenosis should have been considered in the differential diagnosis. It is becoming increasingly recognized that a mild or moderate degree of pulmonary stenosis can be associated with longevity.[2,5] The longest survival time in the series of sixty-eight autopsied patients of Greene and associates[4] was 75 years. The average age in this series was 24 years.

Fig. 6.—Showing fissurelike lesion of the anterior mitral leaflet with thickening and shortening of the chordae tendineae.

The pathological feature was the bicuspid pulmonary valve complicated by rheumatic valvular endocarditis of the aortic, mitral, and tricuspid valves. The degree of stenosis in the aortic valve was advanced. The mitral and tricuspid lesions were only of moderate severity. There was considerable coronary disease with myocardial changes, which we believe played a primary role in the death of the patient. The pathological changes in the liver were moderately advanced and consistent with a far advanced cardiac or portal cirrhosis. This has been described as a feature of pulmonary stenosis by Currens and associates.[6]

SUMMARY

The record of a man with pulmonary stenosis with an intact septum complicated by rheumatic heart disease, who survived to the age of 78 years, has been presented. The longest survival time of a patient with pulmonary stenosis previously recorded was 75 years.

The authors wish to express their gratitude to Dr. Helen B. Taussig for her review of the case history and specimen and for her helpful suggestions.

Fig. 7.—Showing the cuplike depression of the membranous portion of the interventricular septum and stenosis of the aortic valve. The root of the aorta and aortic valve is shown lying to the right of the interventricular septum.

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PERSISTENT PATENT DUCTUS ARTERIOSUS IN THE AGED

Including the Report of the Oldest Case on Record With Diagnosis Confirmed Post Mortem

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SINCE the first successful ligation of a patent ductus arteriosus by Gross and Hubbard in 1939,[1] numerous series of surgical attempts and successes have been reported. Included in these is Gross' series of fifty cases treated surgically with only two operative deaths.[2] The stimulus to surgical correction of this congenital anomaly rests on statistical evaluation of the prognosis of uncomplicated patent ductus arteriosus before this surgical era. For example, in Maude Abbott's 1,000 post-mortem specimens,[3] ninety-seven patients with uncomplicated patent ductus revealed an average age at death of 21 years. Keys and Shapiro,[4] in a reanalysis of sixty autopsied cases reported up to 1943 and limited to adults (17 years of age and over) with uncomplicated patent ductus arteriosus, found the average age at death to be 38.9 years for men and 35.5 years for women, a reduction in life expectancy of 23 and 28 years, respectively.

In 1944, Shapiro[5] reported sixty-two patients with uncomplicated patent ductus arteriosus, some of whom had been followed for eighteen years. Of these patients only three were reported as living beyond 40 years of age. On the basis of this review, he believed that the diagnosis of this condition was an indication for surgical correction as a possible means of lengthening this life span. On the other hand, Wilson and Lubschez, in 1942,[6] recorded thirty-eight cases of this entity followed for as long as twenty years. Of these, only two patients were over 30 years of age at the time of their report. Twenty-two of these patients had not come to autopsy; in two of these the cause of death was given as bacterial endocarditis. In the sixteen autopsies, no instance of congestive heart failure or bacterial endocarditis was found. Their statistics were interpreted as showing that patent ductus arteriosus carries a life expectancy equal to that of most other forms of congenital heart disease, and a life expectancy five times as long as the types of congenital heart disease associated with severe cyanosis. Thus, they felt that uncomplicated patent ductus arteriosus was not a sufficient justification for surgical intervention. Similarly, Benn,[7] on the basis of forty-six patients followed up to 20 years (ages 4 to 31 years), reported only four deaths, each ascribed to bacterial endocarditis. He therefore suggested that bacterial endocarditis, cardiac embarrassment, and retarded physical development should be the only indications for surgery in this condition.

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Patent ductus arteriosus is of further interest clinically, in the possibility of its diagnosis on the basis of ante-mortem findings, and from the standpoint of age attained by the patient with this entity when it remains uncomplicated. Among other considerations in the evaluation of prophylactic ligation are: the more accurate estimation of the symptom-free, living patent ductus population (approximated at 20,000 in the United States by Keys and Shapiro[4]); the possibility of an appreciable number of cases, overlooked at autopsy, when the deaths are noncardiac in nature; the modern chemotherapeutic and antibiotic advances against bacterial endocarditis; and, finally, the significant, however few, reports of longevity attainable with uncomplicated patent ductus arteriosus. White[8] reported the ante-mortem diagnosis and autopsy confirmation of a patent ductus arteriosus in a 66-year-old woman; Josefson[9] reported a 66-year-old white woman, the previously oldest autopsied case on record; and Walker and Ellis[10] reported a case of a living 73-year-old white man with the clinical diagnosis of patent ductus arteriosus.

In the light of these previous reports, two cases of persistent patent ductus arteriosus are recorded in this paper. In the first patient, a 75-year-old woman, the diagnosis was made clinically and was confirmed at post-mortem examination. To the best of our knowledge, this is the oldest patient in which the clinical diagnosis and autopsy confirmation of patent ductus arteriosus were established. The second patient, a 70-year-old white woman, is still living and, at present, is under the observation of our outpatient department.

CASE REPORTS

CASE 1.—M. W., a 75-year-old white woman, was first admitted to Queens General Hospital on Aug. 7, 1949, with a history of good health until approximately two years prior to her admission. Then symptoms of dyspnea and palpitation on effort prompted an irregular digitalis regime. With inconstant therapy, the above symptoms progressed and became complicated by orthopnea and cyanosis six months before admission, and by leg and ankle edema for approximately three weeks prior to admission. Persistence of these symptoms caused her hospitalization.

Her past history included a vague recollection of both chorea and a heart murmur, diagnosed at the age of approximately 10 years.

Physical examination revealed a well-developed, alert, and cooperative woman, orthopneic and cyanotic despite the continuous administration of nasal oxygen. The patient was afebrile with an irregular, rapid pulse of 100, respirations of 26 per minute, and a blood pressure of 210 mm. Hg systolic and 86 mm. Hg diastolic. The head and neck were negative, except for bilateral lenticular opacities precluding funduscopy. Both lung bases, posteriorly, contained equal degrees of moist inspiratory râles. The heart had a totally irregular rhythm, associated with a heaving precordium. The point of maximal impulse was localized to the anterior axillary line in the fifth left intercostal space. A harsh precordial systolic murmur was heard, especially loud at the pulmonic area where it was associated with a thrill and with systolic accentuation. The murmur continued into a long, blowing, early diastolic murmur, the latter best heard at the left sternal border in the second intercostal space and in the pulmonic area. This was not associated with a thrill. A systolic murmur was also heard at the left lung base and over the left scapula.

The liver was enlarged three fingerbreadths below the right costal margin on inspiration. Three plus sacral, pretibial, and ankle edema was present. Subungual cyanosis was noted. No clubbing was seen. The clinical impressions were of an aortic-pulmonary artery fistula, possibly a persisting patent ductus arteriosus with hypertensive heart disease, with both left and right heart failure. The patient was classified as IV E, according to the standards of the New York Heart Association.

On a salt-poor diet, digitoxin, diuretics, and bed rest, the patient became much improved and ambulatory with only a few bibasal râles persisting. Venous pressure was recorded at 80 mm. of water. The circulation times were 7 seconds for arm to lung and 23 seconds for arm to tongue. The hemogram was within normal limits. The blood serology was negative, and the blood chemistry was reported within normal ranges. The chest films revealed generalized enlargement with considerable distension of the pulmonary arteries (hilar). The aortic arch was not widened, but it showed calcification within the knob, thought to be consistent with the patient's age. The greatest transverse cardiac diameter was 15.3 cm.; the intrathoracic diameter was 22.5 cm. Fluoroscopy revealed moderate generalized enlargement of all chambers of the heart with minimal posterior displacement of the barium-filled esophagus. The hilar pulmonary vessels were prominent and bounding; the aorta was not prominently enlarged.

During her hospitalization, the patient developed regular heart rhythm with pulsus alternans. The electrocardiogram at this time revealed left heart strain in a vertical heart with digitalis effect; the rhythm was of regular sinus origin. Phonocardiography was of no further assistance.

The patient was transferred to another hospital for angiocardiography, but this procedure was not undertaken because of the return of evidence of congestive heart failure. The patient was returned to Queens General Hospital for further active treatment. She was observed under the Home Care program for a short time, but she became increasingly dyspneic and orthopneic. She was readmitted to the hospital in March, 1950, but died the day after admission.

Autopsy.—The body was that of an elderly, moderately obese, white woman with the essential findings in the cardiovascular system.

The ductus arteriosus was persistently patent as a shunt between the aorta and the pulmonary artery. Externally, these two vessels were adherent to each other, so that the ductus was markedly shortened and presented as only a bridgelike structure, 2 mm. in length. The aortic orifice measured 3 mm. across and showed a severe degree of atherosclerotic transformation of the surrounding aorta. This was manifest as distinct plaques placed circularly around the opening, giving it a funnel-shaped appearance. The remaining aorta showed only minimal arteriosclerosis. The pulmonary artery orifice was somewhat wider, measuring 4 mm. across, and was also surrounded by considerable arteriosclerotic change of the vessel wall, although the same concentric, conical, narrowing arrangement was not found. The surrounding portions of the pulmonary artery and its major branches showed increased numbers of yellowish-white plaques on its intimal surface.

The heart was enlarged, weighing 600 grams, and showed dilatation and hypertrophy of both right and left sides. The right ventricle was dilated and hypertrophied, the musculature of that chamber averaging 7 mm. in thickness in the region of the conus. The trabeculae carneae were widened and flattened. The left ventricle was hypertensive in configuration with a musculature averaging 12 mm. in thickness. The papillary muscles of this chamber were markedly hypertrophied.

No gross scarring of the myocardium was noted. The coronary vessels showed a minimal to moderate degree of sclerosis compromising their diameters, but patent lumen could be demonstrated in all areas. The aortic valve showed considerable thickening of its cusps with partial fusion at the commissures. The valve cusps were shortened and retracted with irregular, thickened free edges. Superimposed upon this was a moderate degree of calcification, involving the cusps and the valve ring. Though no other evidence of rheumatic disease was found in the heart, the aortic valve distortion seemed rheumatic in origin.

Severe vascular sclerosis was apparent in the other viscera, especially the kidneys. These were shrunken in size, weighing 140 grams each. Their cut surface showed a contracted cortex, averaging 4 mm. in width. Their decapsulated surface presented a uniformly fine granularity and a tannish-brown discoloration.

Both lungs showed some firmness and loss of aeration in their basal portions with a diffuse reddish-purple color to the cut surface in these areas. The cut surface of the liver showed an accentuated tannish-brown lobular architecture with scattered zones of purplish mottling. The spleen was firm and fibrotic. Its cut surface showed a compact purplish-red pulp, which yielded only a small amount of scrapings.

The histological sections confirmed the gross impressions throughout. Severe chronic passive congestion was apparent in the liver, spleen, and kidneys. In addition, the kidneys showed an

Fig. 1.—Aortic side of ductus. Aortic aspect of ductus opening with arrow indicating orifice of funnel-shaped channel, showing considerable atherosclerosis and calcification.

Fig. 2.—Pulmonic aspect of ductus opening indicated by arrow, with pulmonary artery in lower aspect of figure. Note the lessened diameter of this communication in contrast to the larger opening to the ductus found on the aortic side (Fig. 1).

advanced degree of sclerosis, involving primarily the medium-sized arteries in the region of the corticomedullary junction. The lungs revealed severe congestion, thickened alveolar septa, and accumulations of mononuclear histiocytes containing a brown pigment within them. A recent bronchopneumonia was evident by collections of intra-alveolar polymorphonuclear leucocytes.

The final pathological diagnoses included: (1) persistent patent ductus arteriosus; (2) marked dilatation and hypertrophy of the left and right ventricles; (3) arteriosclerotic heart disease; (4) healed rheumatic aortic valvulitis with superimposed calcification; (5) chronic passive congestion of the lungs, liver, spleen, and kidneys; and (5) a recent, patchy bronchopneumonia. The remaining pathological findings were incidental and had no bearing on the essential cardiovascular changes.

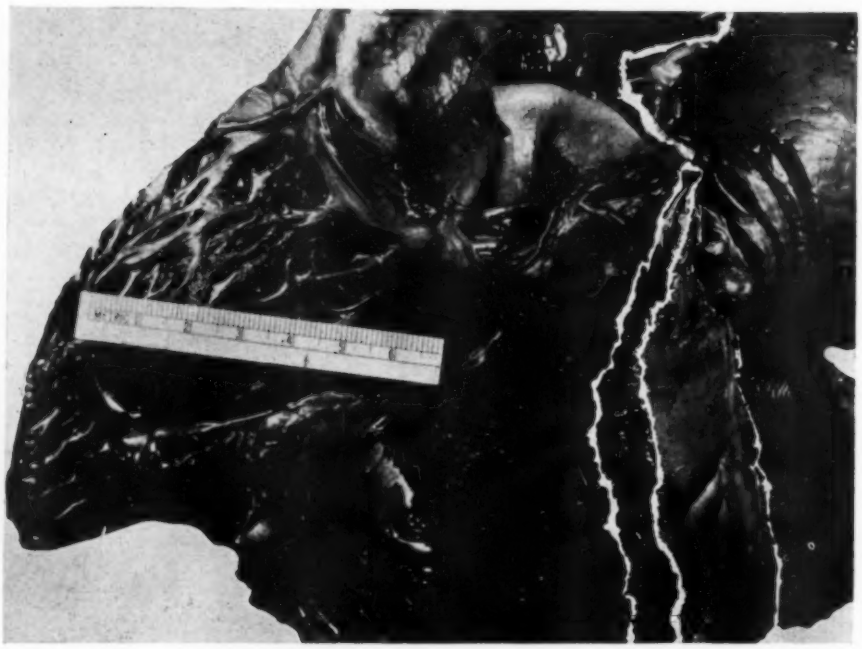

Fig. 3.—Right ventricle, showing dilatation of the chamber and hypertrophy of the wall (retouched to identify thickness of ventricular wall and conus).

CASE 2.—B. F. is a 70-year-old white woman, whose first admission to Queens General Hospital was on Dec. 9, 1949. At that time she complained of nonproductive cough, exertional dyspnea, and rhinorrhea of three weeks duration, following an upper respiratory infection. She had been an ambulatory patient in the outpatient department of the same hospital for the preceding five years for intermittent ankle edema, denying dyspnea, orthopnea, angina, or palpitation before her present three-week illness. Childhood disease, rheumatic fever, and syphilis were denied; she had knowledge of fifteen years of hypertension and recalled a medical examination at the age of 40 years, at which time a cardiac murmur was mentioned with a warning against the danger pregnancy would hold for her. She had one kyphoscoliotic child.

Physical examination revealed a well-developed, 70-year-old, tachypneic woman with intermittent dry cough, temperature of 101° F., pulse rate of 110 per minute, and blood pressure of 160 mm. Hg systolic and 90 mm. Hg diastolic. The head was negative, except for Grade 1 retinal sclerosis. The neck veins were minimally engorged, the carotid arteries equal and bounding. There was moderate senile kyphosis and bibasal medium-moist and crackling râles in the lungs. The cardiac rhythm was totally irregular, the ventricular rate 120 per minute, the sounds of good intensity. The point of maximal impulse was diffusely spread throughout the heaving pre-

cordium, extending to the anterior axillary line and down to the sixth left intercostal space. At the pulmonic area, a Grade 4 long systolic murmur, a systolic thrill, a much diminished second sound, and a long, blowing, low-pitched diastolic murmur were present; these were heard at the third left intercostal space with equal intensity. These combined murmurs were "machinery-like" in quality. Grade 2 systolic murmurs were heard at the mitral and aortic areas; M_1 was louder than M_2, and A_2 was louder than P_2. The liver was felt two fingerbreadths below the right costal margin. Traces of pedal edema, but no clubbing, were found; increased capillary pulsations were demonstrable. Good femoral pulsations were noted. The diagnoses of patent ductus arteriosus, arteriosclerotic heart disease, and hypertensive heart disease were made.

The hemogram, blood chemistry, and urinalysis were normal, except for 2 plus albuminuria. The serology was negative. On fluoroscopy, generalized enlargement of all chambers of the heart was noted; no conspicuous displacement of the barium-filled esophagus was found. The left hilum was bounding, and the pulmonary artery and conus segments were prominent. The electrocardiogram revealed auricular fibrillation with left ventricular preponderance. The venous pressure was 120 mm. of water. The circulation times were 22 seconds arm to tongue (saccharin) and 5 seconds arm to lung (ether).

On a salt-free diet, digitoxin, and mercurial therapy, the patient became compensated and was discharged on Dec. 27, 1949. She was readmitted on Feb. 14, 1950, for recurring dyspnea and was treated with similar success. On March 14, 1950, the patient was transferred to another hospital for angiocardiography; however, her condition was considered unsuitable for such study, and the patient was discharged with the diagnosis of patent ductus arteriosus confirmed by other clinical observers. She is at present again under the care of the Queens General Hospital Outpatient Department.

DISCUSSION

The recent advances in the technique and feasibility of cardiac surgery, especially relative to ligation of a patent ductus arteriosus, have focused attention on this entity and its prognostic implications. In an attempt to determine the value of early surgical ligation as opposed to a nonoperative regime, several statistical analyses of patients with this condition have been made. In the earlier reports, these data concerned themselves with the presentation of children and young adults, with an attempt to contrast the life expectancy of these patients with patent ductus arteriosus with that of a group of normal patients representing a cross section of the population in that age group. More recently, emphasis has been toward noting instances of adults who have lived to or beyond the expected life span.

On the basis of these surveys, it was generally accepted that complications of a patent ductus arteriosus might constitute definite indications for ligation. These included the appearance or the impending onset of congestive heart failure, retardation of physical growth and development, and the presence of bacterial endocarditis in the region of the ductus. The latter complication was formerly such a formidable one and associated with such severe prognostic significance that the mere possibility of its occurrence was, to some observers, a sufficient warrant for prophylactic ligation. In the review of Keys and Shapiro,[4] for example, subacute bacterial endocarditis and congestive failure were listed as the cause of death in forty-two (70 per cent) of the reported cases. More recently, antibiotic therapy has markedly altered this prognostic outlook.

Uncomplicated patent ductus arteriosus, however, has never constituted such a generally accepted indication for operative correction. More definite division of thought exists here between advocates of surgical and nonsurgical

management. It is in an attempt to clarify further the prognostic aspects of uncomplicated patent ductus arteriosus that reports of its presence in the elderly have been made.[8,9,10]

The first case reported in this paper is the oldest known patient with a persistent patent ductus. The patient enjoyed good health until the age of 73 years, two years before her death, when she first manifested increasing objective and subjective symptoms of decompensation. These symptoms responded favorably to an accepted cardiac regime, but recurred when the patient's activity became too great.

The diagnosis of patent ductus arteriosus, made on the basis of clinical findings, was confirmed on post-mortem examination in the first patient. In accord with the statistical analysis of Keys and Shapiro,[4] the heart in this instance showed great enlargement, with equal relative hypertrophy of both left and right ventricles. In four of their forty-six cases, similar findings were apparent. These authors noted that ten of their sixty patients (17 per cent) with persistent patent ductus arteriosus showed a markedly shortened ductus segment in adults, which would have made any surgical attempt at ligation either extremely difficult or impossible. They also stated that in the usual instance the aortic orifice of the ductus is funnel shaped and larger than the pulmonary artery orifice. Both these criteria were apparent in the autopsied case, except that in this instance, although the aortic side of the ductus was funneled, the cross diameter of the ductus proper was smaller than that at the pulmonary aspect.

On the basis of previously reported cases, the size of the persistent patent ductus arteriosus may be an important factor in determining the eventual prognosis of the patient, regarding both the development of complications and the estimation of life expectancy. Keys and Shapiro,[4] in their accumulated review of sixty-seven cases, noted the age of the patient, the size of the ductus, the size of the heart, and the cause of death, in those cases where these facts were available.

In general, no accurate correlation could be demonstrated between the diameter of the ductus arteriosus and the incidence of congestive heart failure. For example, two patients were cited, each of whom died in congestive failure at the age of 23 years, who showed large aorta-pulmonary artery shunts; however, one instance was cited in which the bore of the ductus shunt was 12 mm., and yet the patient survived to 47 years before succumbing to cardiac failure. Conversely, the smallest diameter ductus, among those who died in congestive failure, was seen in a patient 32 years old. The three most elderly patients included in the review—66, 66, and 65 years of age, respectively—showed relatively large passages, each measuring 4 mm. in diameter at the pulmonic aspect and 9 to 10 mm. across at the aortic side.

A much closer correlation existed in these tabulated cases between the diameter of the ductus and the size and hypertrophy of the right ventricle. Thus, in those instances where the bore was small, irrespective of age, the right ventricle was either only slightly hypertrophic or not at all; in a few of these instances the right ventricle showed only dilatation without hypertrophy.

Almost without exception, in those instances where the diameter of the shunt was large, right ventricular hypertrophy existed.

The present autopsied case showed hypertrophic enlargement of both left and right ventricles, the former to a thickness of 7 mm. and the latter to a thickness of 12 mm. The left ventricular hypertrophy was presumably secondary to nephrosclerosis and hypertension. The presence of an audible murmur and the evidence of right ventricular hypertrophy at autopsy were indications that the ductus had been functioning in this case, despite the relatively small diameter of the lumen.

SUMMARY

The increasing interest in the surgical correction of patent ductus arteriosus has led to several surveys of the relative prognosis in both operated and nonoperated cases. A persistent patent ductus in a 75-year-old woman is presented as the oldest case on record with both ante-mortem and autopsy diagnoses. This patient enjoyed active health until the age of 73 years, at which time evidence of congestive heart failure first appeared. In common with previous observations,[4] evidence of heart failure, once initiated, was persistent and recurred with increasing severity, despite several remissions under cardiac regimen. The final episode of failure in the first patient was complicated with a bronchopneumonia. In that instance, the clinical impression of a persistent patent ductus arteriosus was confirmed at autopsy, showing a shunt 3 mm. in diameter at the aortic side and 4 mm. in diameter at the pulmonic orifice, associated with considerable hypertrophic enlargement of the right ventricle. The second case is of interest as another patient with uncomplicated patent ductus among the oldest cases reported. Both patients were admitted to the same hospital ward within a five-month period.

Previous authors have stressed the necessity of reporting such cases of persistent ductus arteriosus in adults in an attempt to evaluate further its prognostic significance and compatibility with long life.

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CONGENITAL VENTRICULAR SEPTAL DEFECT WITH ACQUIRED COMPLETE HEART BLOCK

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THE association of some congenital cardiac anomalies, particularly ventricular septal defects, with complete heart block is well established. It is the purpose of this report to present the clinical and pathologic observations of a case of congenital ventricular septal defect and acquired complete heart block. The diagnosis of congenital ventricular septal defect was made clinically and confirmed at necropsy. Normal conduction with sinus rhythm was present until the fourth year of life, when complete atrioventricular dissociation and idioventricular rhythm, accompanied by Adams-Stokes attacks, developed. Death occurred during one of the Adams-Stokes episodes, when the patient was 4½ years of age.

CASE REPORT

Clinical Features.—The patient was a white boy, 2½ years of age at the time of his first examination by one of us (C.C.R.), on March 20, 1947. The child had been born normally at full term. The mother had experienced no infections during her pregnancy. Both parents suffered from chronic alcoholism. The mother stated that she had drunk excessively during the first three months of her pregnancy.

No abnormal cyanosis had been observed at birth, but respiration was established with difficulty. During the first two years of life there was no cyanosis. There had been no childhood infections. There had been no restrictions of physical activity, and the child had developed normally. The mother noted that with exertion the child tired easily and dyspnea occurred.

Physical examination revealed an active child. There was no dyspnea or cyanosis. The pulse rate was 100 per minute and regular in rhythm. The blood pressure was 100 mm. Hg. systolic and 80 mm. Hg. diastolic. The pertinent physical findings were confined to the cardiovascular system. There was a Grade 3 systolic murmur (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition) of maximal intensity at the third left intercostal space, but this murmur was widely transmitted over the entire precordium, as well as to the mitral, aortic, and pulmonic areas. Transmission of the murmur to the back also occurred. There was a systolic thrill at the third and fourth left intercostal spaces, most intense to the left of the sternum. The abdomen was normal. The extremities were normal with no clubbing of the digits. The femoral pulses were palpable.

Erythrocytes numbered 4,850,000 per cubic millimeter of blood, and the hemoglobin was 84 per cent or 14.2 Gm. per 100 c.c. of whole blood. Leucocytes numbered 11,250 per cubic millimeter of blood. The differential leucocyte count revealed 26 per cent polymorphonuclear leucocytes, 62 per cent lymphocytes, and 2 per cent eosinophils. An electrocardiogram revealed normal sinus rhythm (Fig. 1). The auricular and ventricular rates were 120 beats per minute. The P-R interval measured 0.16 second and the QRS complex 0.08 second. The T wave in Lead III was inverted. A roentgenogram of the thorax revealed clear pulmonary fields. There was marked prominence of the left side of the heart, the left border having a rounded outline. The apex lay

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above the diaphragm, giving a characteristic wooden shoe appearance to the cardiac silhouette. The clinical diagnosis of congenital cardiac disease with probable ventricular septal defect was made.

The child's subsequent course was uncomplicated for one and one-half years. There were no no intercurrent infections. Normal activity during this period was permitted. No dyspnea was observed except with fast walking. At no time was cyanosis observed.

On Jan. 8, 1949, twenty-one months after the original examination, the patient, 4 years of age, was again observed. An attack of fainting, vertigo, and unconsciousness for a period of several minutes had occurred shortly before this examination. The physical examination at this time revealed the pulse rate to be 48 per minute. The blood pressure was 120 mm. Hg. systolic and 80 mm. Hg. diastolic. With the exception of the bradycardia, examination of the heart gave results similar to those recorded for the earlier examination. The results of examination of the lungs, abdomen, and extremities were unchanged.

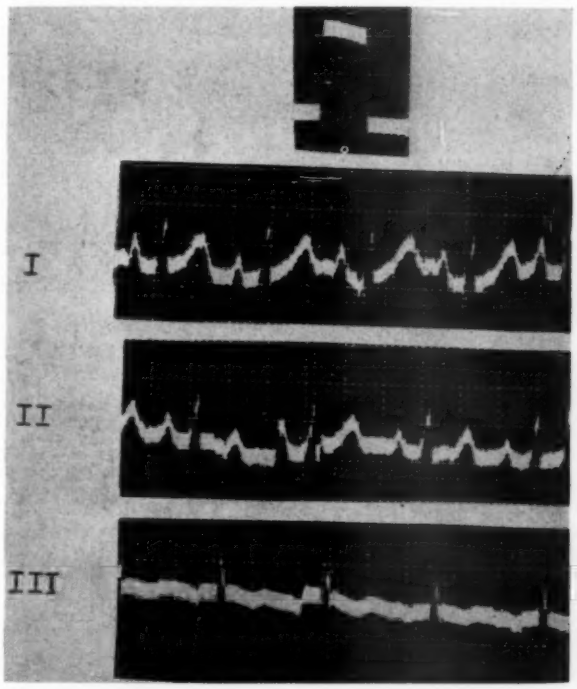

Fig. 1.—Electrocardiogram taken on April 10, 1947. Ventricular septal defect. Sinus rhythm with normal atrioventricular conduction.

The electrocardiogram now revealed complete heart block (Fig. 2). The ventricular rate was 50 beats per minute and the auricular rate was 110 beats per minute. The T waves in CF_4 were deeply inverted. Premature ventricular beats were present. A roentgenogram of the chest revealed an increase in cardiac size. The cardiac measurements were maximum right, 2.6 cm.; maximum left, 7.1 cm.; transverse thoracic diameter, 16.8 cm. The cardiothoracic ratio was 57.7 per cent. The aortic knob was not visualized (Fig. 3). There was obliteration of the retrosternal space in the lateral roentgenograms. The diagnosis of acquired complete heart block secondary to congenital ventricular septal defect was made.

During the subsequent six months, persistent complete heart block was observed with recurrent attacks of Adams-Stokes syncope. Electrocardiographic readings were not obtained during an attack, but attacks were accompanied by short periods of ventricular asystole, as deter-

mined by palpation of the pulse and cardiac auscultation. Death occurred suddenly in August, 1949, during an attack of Adams-Stokes syncope.

Necropsy Findings.—At necropsy the pertinent findings were confined to the heart and great vessels. The heart, which was slightly enlarged, weighed (with the aorta and the trachea attached) 100 grams. The weight of a normal heart from a child 4 years old is approximately 65 grams. There was a large defect involving the membranous portion of the ventricular septum. The defect measured 1.6 cm. from above downward and 1.5 cm. from behind forward. Viewed from the left ventricular aspect, the defect lay immediately beneath the aortic valve (Fig. 4,*a*). From the right ventricular aspect (Fig. 4,*b*) the defect was closely associated with the septal leaflet of the tricuspid valve. Some of the chordae tendineae of the septal leaflet of the tricuspid valve were inserted into the muscular part of the ventricular septum on the left ventricular side (Fig. 4*a*).

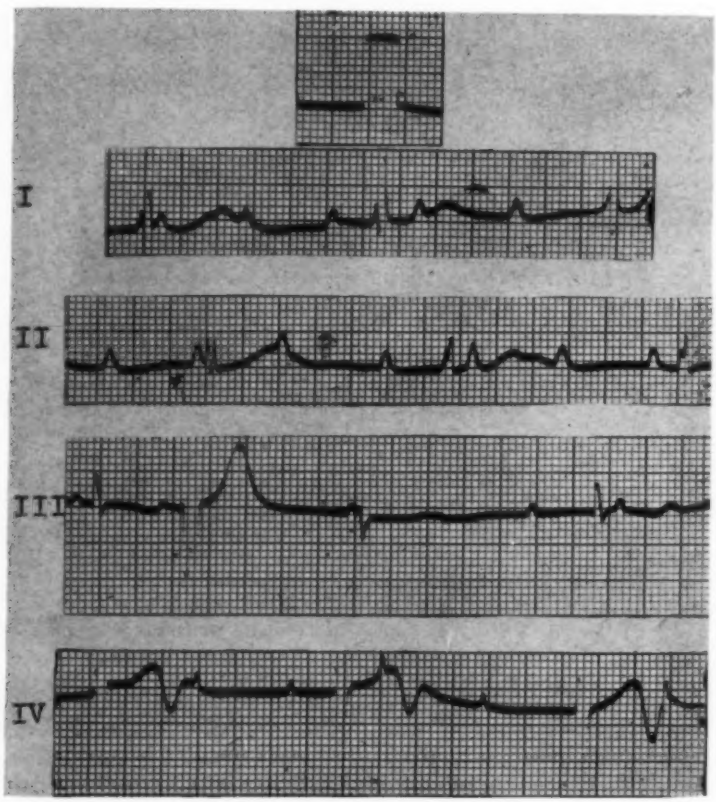

Fig. 2.—Electrocardiogram taken on Jan. 11, 1949. Ventricular septal defect. Complete heart block. A premature ventricular beat is present in Lead III.

In this way, the defect was somewhat reduced in size by the location of the septal tricuspid leaflet. The size of the defect was reduced to 1 cm. in an anteroposterior plane. The lower margin of the defect was crescent-shaped and was bordered by the muscular part of the ventricular septum. Though the aortic origin was closely associated with the ventricular septal defect, the aorta arose exclusively from the left ventricle. The aorta was relatively wide, measuring 3.2 cm. in circumference. The aortic valve had three normal leaflets. The coronary arteries arose in a normal manner.

The pulmonary trunk, in contrast to the aorta, was narrower than normal, measuring 2.2 cm. in circumference. The pulmonary valve was represented by three leaflets. The right and left

leaflets were somewhat thickened but of normal size, while the anterior leaflet was smaller than either of the other two (Fig. 4,*c*). There was a normal difference between thicknesses of the two ventricles. The left ventricle, which was dilated, measured 6 mm. in thickness, while the right ventricle measured 3 mm. in thickness. The tricuspid valve was normally formed, except for the insertion of part of the chordae tendineae of the septal leaflet into the left ventricular side of the ventricular septum, as already mentioned. The mitral valve was normally formed. The great veins entered the atria in normal fashion. The foramen ovale was patent to a probe.

There was an associated malformation of the aortic arch system. The aortic arch passed over the right instead of the left bronchus and joined the descending aorta at about the midline, just behind the esophagus (Fig. 4,*d*). From this location the descending aorta departed to the left. Four branches arose from the upper thoracic aorta. The first branch was the left common carotid artery, the second was the right common carotid artery, and the third branch was the right subclavian artery. The left subclavian artery arose from the left side of the aorta at the level of the junction of the aortic arch with the descending aorta. The upper portion of the ligamentum arteriosum was inserted into the base of the left subclavian artery, while the lower portion of the ligamentum arteriosum was attached to the left pulmonary artery.

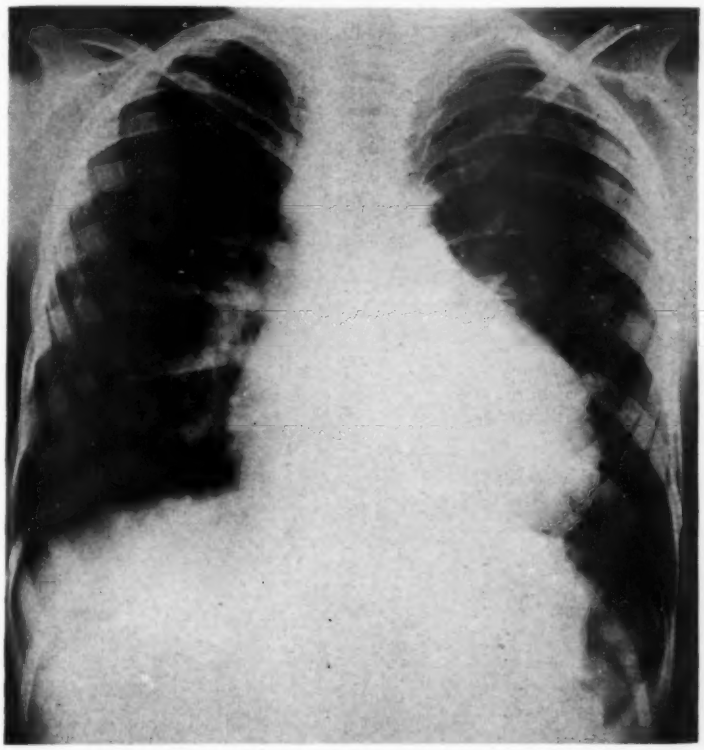

Fig. 3.—Roentgenogram of the chest. Left ventricular enlargement.

The aortic malformation created a vascular ring about the esophagus and the trachea. On the right the ring was formed by the right aortic arch, in back by the junction of the aortic arch with the descending aorta, on the left by the ligamentum arteriosum, and in front by the bifurcation of the pulmonary trunk.

The following gross anatomic diagnoses were made: (1) ventricular septal defect, (2) moderate pulmonary stenosis, and (3) vascular ring about the esophagus and trachea. The association of a ventricular septal defect and pulmonary stenosis raises the question whether a tetralogy of

Fallot existed. It is not probable that this case should be classified as a tetralogy of Fallot, for the aorta arose exclusively from the left ventricle and the right ventricle was not thickened.

Histologic examination of both ventricles, both atria, and the mitral and tricuspid valves revealed no evidence of preceding rheumatic infection. A section from the upper part of the ventricular septum, including the margin of the septal defect, revealed a minimal amount of fibrous thickening of the endocardium, but no extension of the fibrous connective tissue into the underlying muscle. The myocardium was normal.

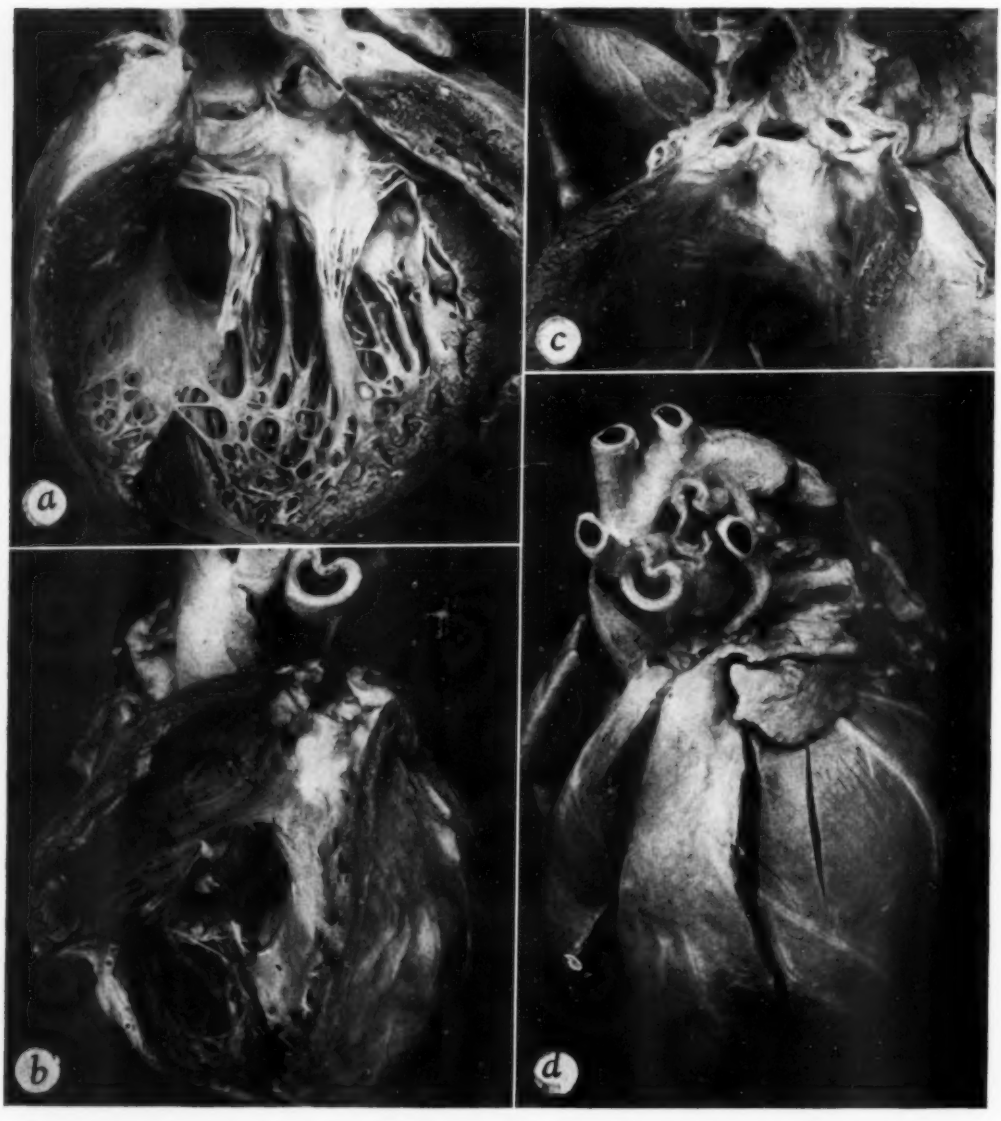

Fig. 4.—*a*, Interior of left ventricle. Defect in the membranous portion of the ventricular septum. Insertion of chordae tendineae from the septal leaflet of the tricuspid valve onto the left ventricular side of the ventricular septum. *b*, Interior of right ventricle. Ventricular septal defect and right ventricular outlet tract. *c*, Pulmonary valve in the opened state. *d*, Heart, anterior aspect. Right aortic arch with vascular ring surrounding the esophagus and trachea. There is a left ductus arteriosis (closed) inserting into the left subclavian artery, which originates as the fourth branch of the aorta.

COMMENT

Complete heart block associated with congenital heart disease is not common. In 1933, Yater, Lyon, and McNabb[1] accepted forty-four cases of congenital heart block in an extensive review of the literature. Cases of congenital heart block studied at necropsy are infrequent. Wallgren and Winblad,[2] in 1938, reviewed the literature on congenital heart block and reported two cases of their own studied at necropsy. At this time the total number of patients examined at necropsy was eleven. While congenital heart block is most often associated with a ventricular septal defect, it has also been recorded as existing with other congenital cardiac anomalies, including cor triloculare biatriatum,[1,3] complete transposition of the great vessels,[3] patent ductus arteriosus,[4,11] absent atrial septum,[5] and tricuspid atresia.[6]

The association of congenital cardiac disease with acquired complete heart block is much less common than its association with congenital complete heart block. Acquired heart block dependent upon a congenital cardiac anomaly has been reported in two previous instances by Laubry and Pezzi[7] and by Yater, Barrier, and McNabb.[8] Waldman,[4] in 1945, recorded a case of probable patent ductus arteriosus with mild Adams-Stokes attacks due to a transient heart block interrupting a normal rhythm.

It has been suggested by Burchell[9] that complete congenital heart block may be an acquired traumatic leasion developed in utero. The case reported herein suggests that roles may be played by acquired factors in the causation of heart block in congenital cardiac disease. Waldman has emphasized that theoretical physiologic considerations, related to pressure, tension, or circulatory changes affecting the bundle and interfering with its conductivity, may explain the reasons for the fluctuation in the conductivity of the bundle. Brown stated: "It appears likely that for reasons of strain heart block may be acquired in a congenital lesion."

In considering the basis for the acquired complete heart block in the present case of ventricular septal defect, it is important to emphasize that microscopic examination of the lower margin of the defect showed no extension of endocardial fibrous tissue into the underlying muscle. It is also important that no lesion was found histologically in the muscle at the anticipated location of the bundle. Therefore, two possible causes of complete heart block are ruled out.

It may be that mechanical factors, including changes in pressure and tension of the bundle, contributed to the development of the complete heart block. It can be postulated that, as the heart grew, enlargement of the septal defect occurred and so may have resulted in an increase in the concave shape of the lower margin of the septal defect. This in turn could have caused compression of the septal myocardium and the resultant conduction disturbance.

The case reported herein is unusual in that acquired heart block developed in a patient with congenital ventricular septal defect. The only comparable cases that we can find in the literature are those recorded by Laubry and Pezzi,[7] and by Yater, Barrier, and McNabb.[8] Waldman's case of paroxysmal heart block occurred in association with clinical evidence of patent ductus arteriosus.

In addition to the coexistence of acquired complete heart block with ventricular septal defect, the Adams-Stokes syndrome developed in our patient.

SUMMARY

A case of congenital ventricular septal defect and acquired complete heart block is presented. When first examined at 2½ years of age, the patient had normal atrioventricular conduction. At the age of 4 years persistent complete heart block developed. This was accompanied by Adams-Stokes attacks. Death occurred during an attack of Adams-Stokes syncope. The association of acquired complete heart block with congenital cardiac disease is very uncommon.

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FATAL MYOCARDIAL SARCOIDOSIS

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NEWINGTON, CONN.

BERNSTEIN and associates[1] first described sarcoid lesions in the myocardium and epicardium in 1929. In 1935, Salvesen[2] postulated the presence of a myocardial nodule in a patient who had sarcoidosis and bundle branch block alternating with a regular rhythm, but proof of this was impossible in the absence of an autopsy. In the following year, Schaumann[3] reported some epicardial lesions and, in 1937, Nickerson[4] reported myocardial lesions in a 58-year-old Negro woman who died of acute sarcoidosis. These lesions, as well as those described in the following cases, were found at autopsy. In 1939, Cotter[5] reported a case of myocardial involvement in a 19-year-old Negro man who died of cardiorespiratory failure. In 1941, Longcope[6] reported a case of myocardial sarcoid in a 40-year-old Negro man who died suddenly and a second case in a 42-year-old Negro man with a story of chronic heart disease, who committed suicide and in whom the presence of a positive Wassermann reaction and a septal scar clouded the issue. In 1944, Johnson and Jason[7] reported a case of death due to myocardial sarcoid in a 24-year-old Negro man. In 1948, Bates and Walsh[8] and Scotti and McKeown[9] each reported a case of sudden death due to myocardial sarcoid in young Negro men aged 31 and 26 years, respectively. Ricker and Clark,[10] in 1949, reported a case of sudden death in a 24-year-old Negro man with myocardial sarcoid. In 1950, Kulka[11] reported a case of sudden death due to myocardial sarcoid in a 26-year-old Negro woman. Of these eight cases of death due to myocardial sarcoid all had occurred in Negroes, predominantly in young men, and more than half had died suddenly. Other cases of cardiac sarcoid in which death was not due to the heart lesions were those of Spencer and Warren,[12] Longcope,[6] Skavlem,[13] and Hauser.[14] The following case report is the first case of death due to this condition that has been reported in a white man.

CASE REPORT

A 51-year-old, white, male meatcutter entered another hospital in 1946 with a transient episode of bilateral parotitis and left facial paralysis, the etiology of which had been undetermined. He had had a chronic cough for many years productive of small amounts of mucoid

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sputum. Roentgenograms of the chest at that time showed bilateral hilar adenopathy, widening of the superior mediastinum, and linear infiltration of the right lower lobe. The heart silhouette was normal (Fig. 1). Two and a half years later, he developed progressive weakness, easy fatigability, dyspnea even at rest, and mild orthopnea. Digitalis, 0.1 Gm. daily, gave no relief.

He was admitted to Newington on May 3, 1949. Temperature was 98.6° F., pulse 86, blood pressure 130/84 mm. Hg, and respiratory rate 26. His chest was emphysematous. Mediastinal dullness was slightly increased at the level of the second and third intercostal spaces. Râles were present at both bases. The heart was enlarged to the left, and a presystolic gallop was present at the apex. The liver was palpable 4 cm. below the right costal margin. The rest of the physical examination was essentially normal. Laboratory studies, including white cell count and differential, erythrocyte sedimentation rate, hemoglobin, serum protein, blood urea nitrogen, cholesterol, urines, Mazzini, and repeated sputum examinations for acid-fast bacilli, revealed no abnormalities. Purified protein derivative skin tests were negative. Roentgenograms of the chest showed a moderately enlarged heart with elongation of the left ventricular contours, widening

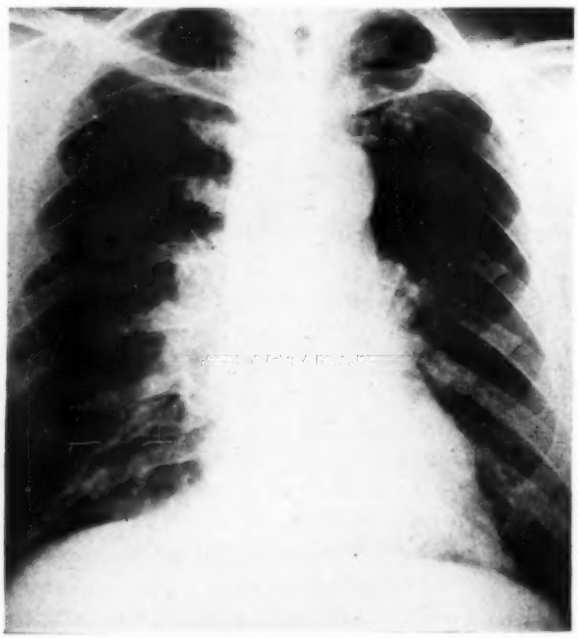

Fig. 1.—Chest film taken on Aug. 19, 1946, during an episode of transient "bilateral parotitis" showing bilateral hilar adenopathy, widening of the superior mediastinum, and linear infiltration of the right lower lobe. The cardiac silhouette is normal.

of the superior mediastinal shadow, pulmonary congestion, and minimal interstitial fibrosis. On fluoroscopy there was found to be an enlarged left ventricle with almost normal pulsations, absent right cardiac pulsations, and a homogeneous density in the anterior superior mediastinum. Electrocardiograms revealed low voltage in the limb leads, normal sinus rhythm, a P-R interval of 0.24 second, T_1, T_2, T_{AVF} low inverted, T_{AVL} flat, T_{V4}, T_{V5}, T_{V6} inverted, ST_{V1}, ST_{V2}, ST_{V3} depressed. The form of the QRS complexes indicated an intermediate heart with slight clockwise rotation (Fig. 2). Venous pressure in an antecubital vein at the level of the right auricle was 20 cm. of water, and arm to tongue circulation time was 23 seconds. During six weeks in the hospital on digitoxin, 0.1 mg. daily, bed rest, and a salt-free diet, the patient remained afebrile and had less dyspnea, associated with a 9 pound weight loss, disappearance of râles, and a decrease in the size of the liver. Subsequent electrocardiograms showed reversion of T_{V4}, T_{V5}, T_{V6} to upright without change in voltage or ST segment shifts (Fig. 2).

He was admitted for the last time on Sept. 9, 1949, in profound congestive failure, with paroxysmal nocturnal dyspnea, abdominal swelling with shifting dullness, and pedal edema. Temperature remained between 100 and 101° F. throughout the three-week hospital course, returning to normal three days prior to his death. His pulse rate ranged between 80 and 100 until the last two days. The respiratory rate was 40. Râles were again present over both bases, and a presystolic gallop was present. The liver edge was palpable 9 cm. below the right costal margin. The area of dullness in the upper mediastinum was widened, and electrocardiograms showed an increase in clockwise rotation (Fig. 2). Roentgenograms revealed the heart to be greatly enlarged both to the left and right, with pulmonary congestion and bilateral pleural effusion (Fig. 3).

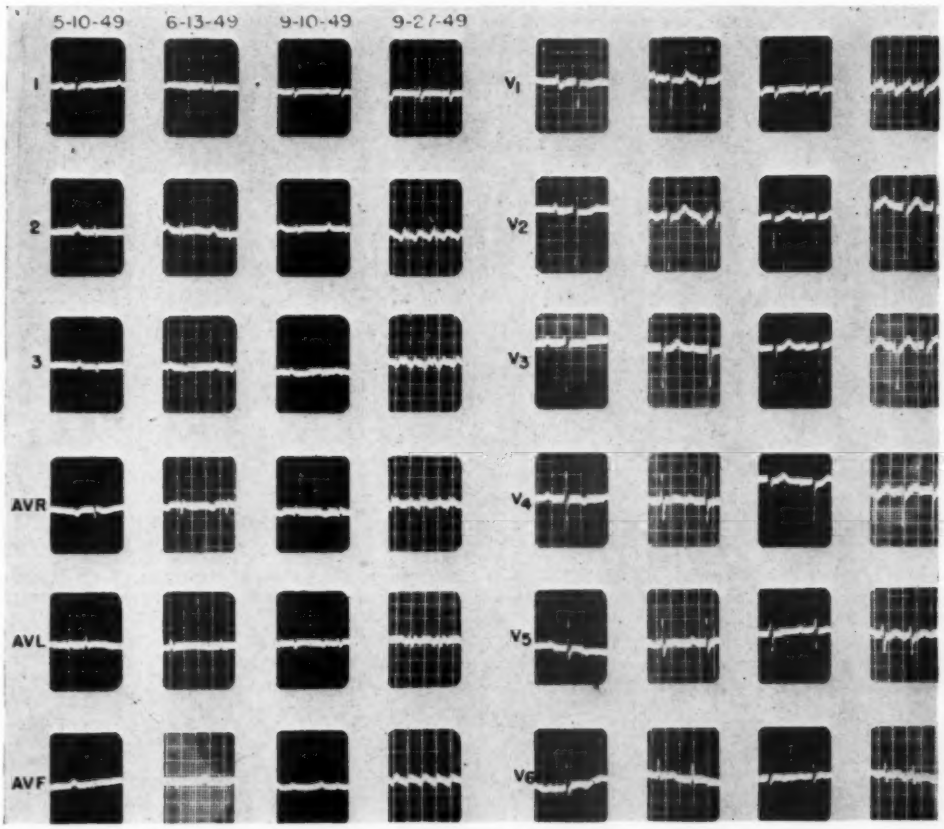

Fig. 2.—Serial electrocardiograms from the time of the first admission until the day before death, showing persistent first-degree auriculoventricular block, varying S-T changes including clockwise rotation, and finally auricular flutter.

On bed rest, oxygen, low sodium diet, digitoxin, mercurial diuretics, and penicillin, there was no diminution of dyspnea, weakness, or fever. On September 27 he was found to have auricular flutter with a ventricular rate of 130 per minute (Fig. 2). After 2.5 Gm. of quinidine over a twelve-hour period the rhythm reverted to a sinus tachycardia with varying first-degree auriculoventricular block, a marked degree of nonspecific intraventricular conduction delay with a QRS interval of 0.16 second, and low to absent initial R waves over the entire precordium (Fig. 4). He died in cardiovascular failure on Sept. 28, 1949.

Autopsy Report.—Anasarca was present. The pleural surfaces of both lungs were studded with tiny, pink-gray nodules, 1 to 5 mm. in diameter, both single and confluent (Fig. 5). Thick,

fibrous adhesions and a fine, fibrinous exudate were present bilaterally. Fine nodules were palpable throughout both lungs. On section these were most prominent in the pleura and subpleural parenchyma. The mediastinal lymph nodes were enlarged, firm, and rubbery, with complete loss of architectural pattern but without disruption of the capsules. The heart was considerably enlarged, weighing 600 grams. Fibrinous exudate was present on the epicardium at the apex of the left ventricle, which was otherwise of normal appearance. The right ventricle was both

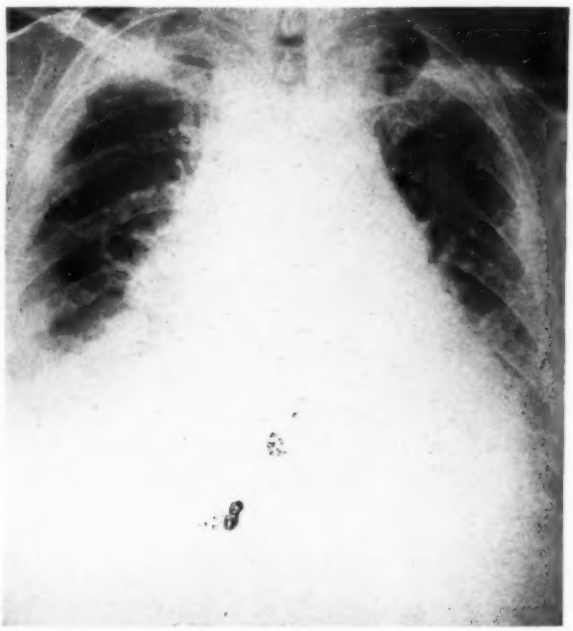

Fig. 3.—Chest film taken on Sept. 15, 1949, during the last admission, showing bilateral pleural effusion, widening of the hilar and mediastinal shadows, linear streaking of the parenchyma, and cardiac enlargement.

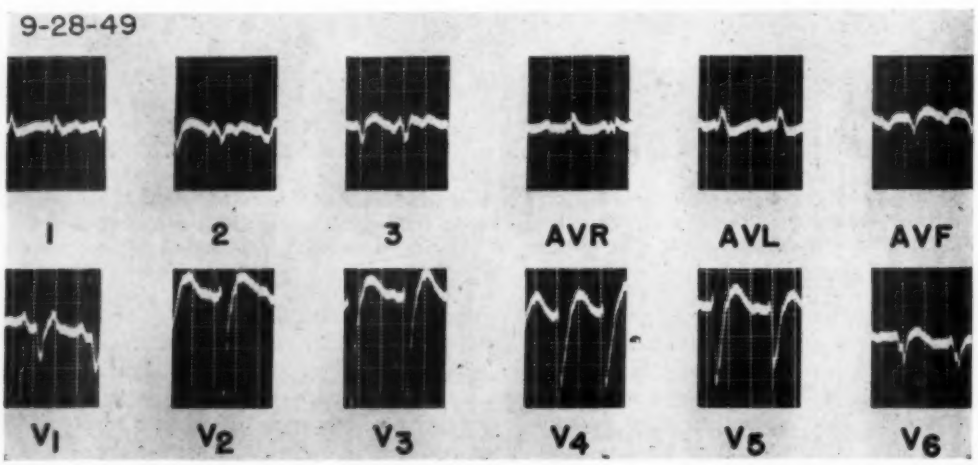

Fig. 4.—Electrocardiogram taken on the day of death, following the administration of quinidine demonstrating a reversion to normal sinus rhythm with first-degree auriculoventricular block and a severe diffuse intraventricular conduction defect.

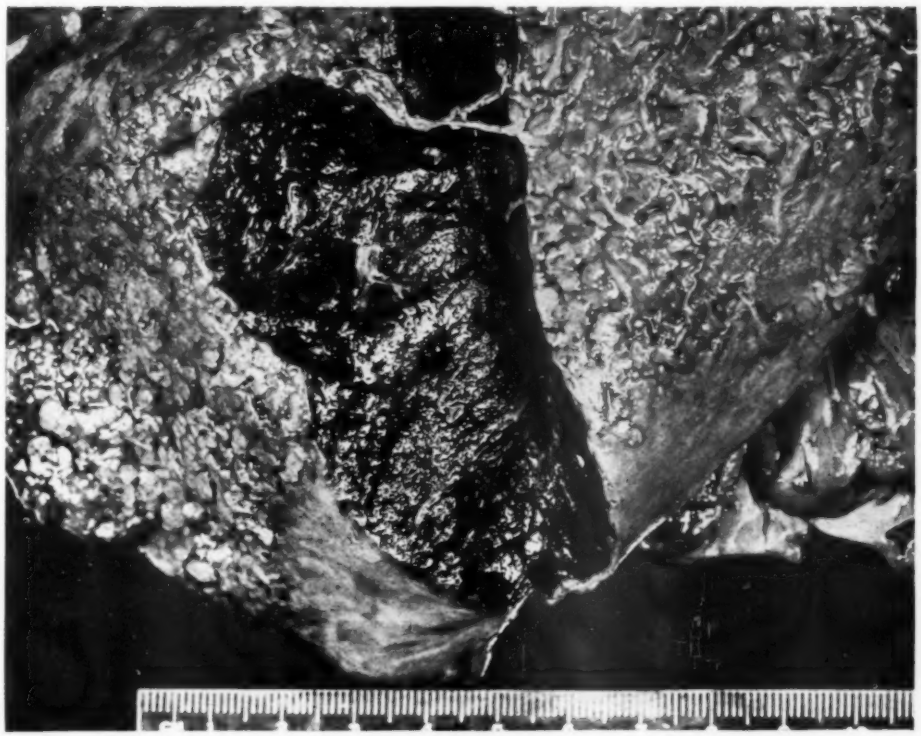

Fig. 5.—Pleural surface of lung, showing numerous discrete and confluent sarcoid tubercles.

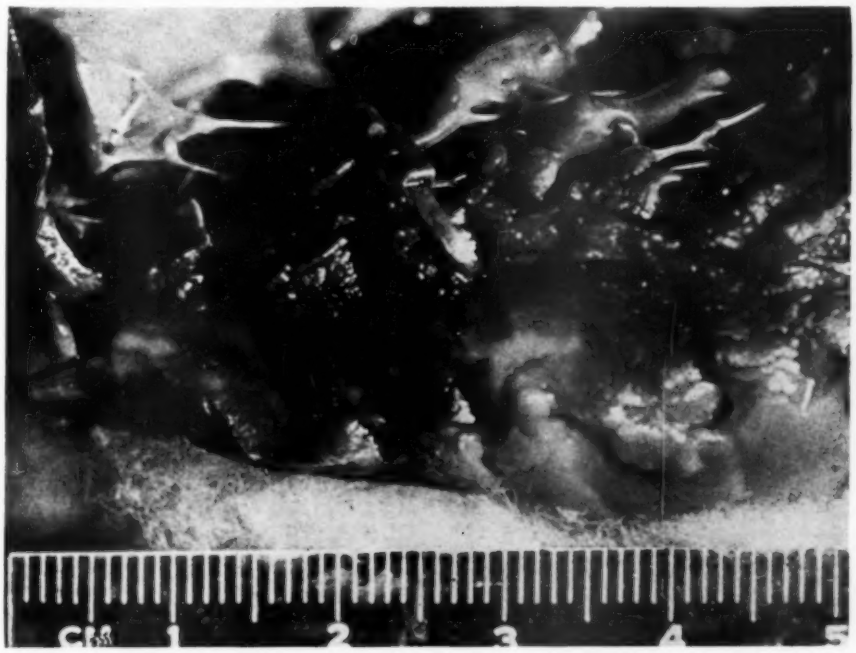

Fig. 6.—Left ventricular myocardium, showing large irregular sarcoid granulomata, appearing as gray-white areas.

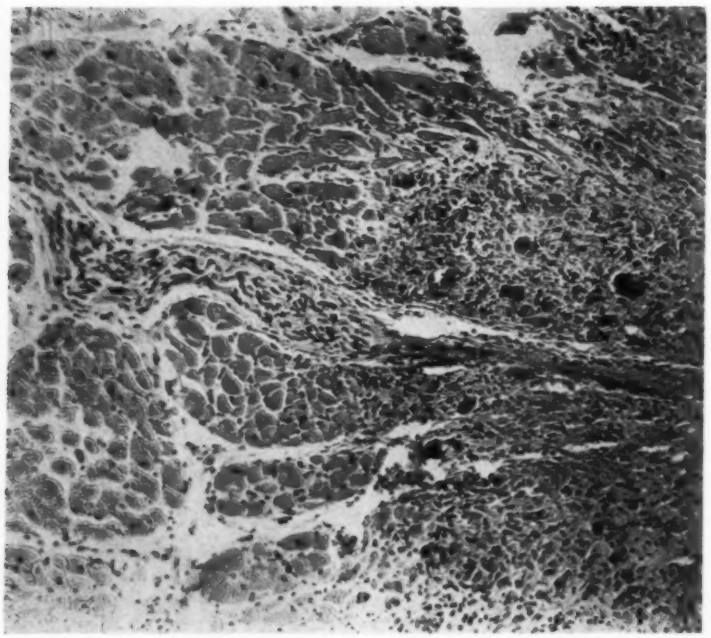

Fig. 7.—Photomicrograph, 150×, showing sarcoidosis of myocardium. Note nerve bundle entering granulomatous process.

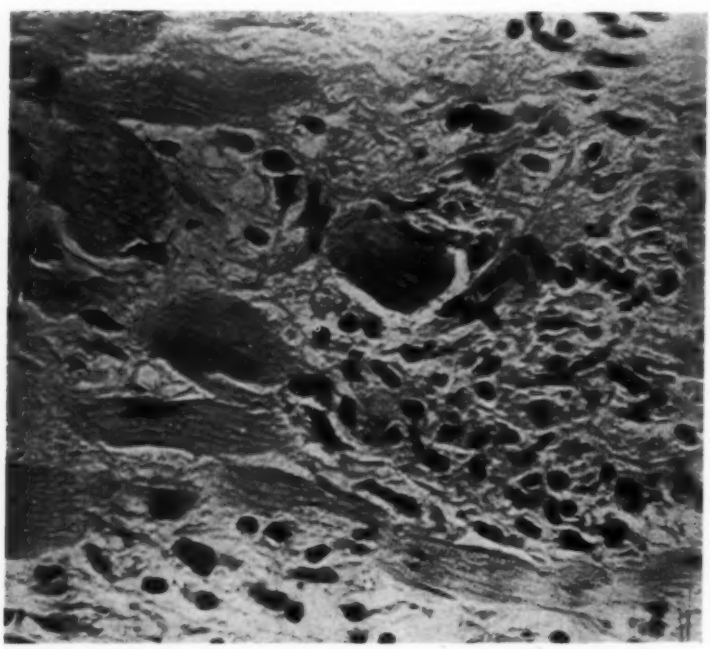

Fig. 8.—Photomicrograph, 600×, showing detail of edge of granuloma.

dilated and hypertrophied, its wall measuring 10 mm. in thickness. The valves were normal. Numerous small, gray-white, discrete, irregular areas, averaging about 4 mm. in diameter, were visualized throughout the myocardium of both ventricles and in the interventricular septum (Fig. 6). The left coronary artery was markedly sclerotic and calcified. About 3 cm. from its ostium, it was markedly calcified and stenotic but not completely occluded. The spleen, liver, gall bladder, pancreas, adrenals, gastrointestinal tract, genitourinary systems, and bone marrow were all grossly normal. The pleural nodules and mediastinal nodes were cultured and injected into guinea pigs with negative results.

Microscopically, there was widespread occurrence of granulomata in the lungs, heart, lymph nodes, spleen, liver, pancreas, and thyroid. They varied from simple epithelioid cell collections to completely hyalinized, collagenous connective tissue. The unscarred lesions, which tended to be well demarcated, consisted essentially of epithelioid cells and giant cells and were located predominantly in the peritruncal tissue in the lungs. The giant cells, scattered haphazardly through the granulomata, were large and had many nuclei, as many as 100 being visible in a single cell. Numerous capillaries were closely appliqued to individual lesions, sometimes actually entering them. No significant degree of central necrosis was noted. Lymphocytes, plasma cells,

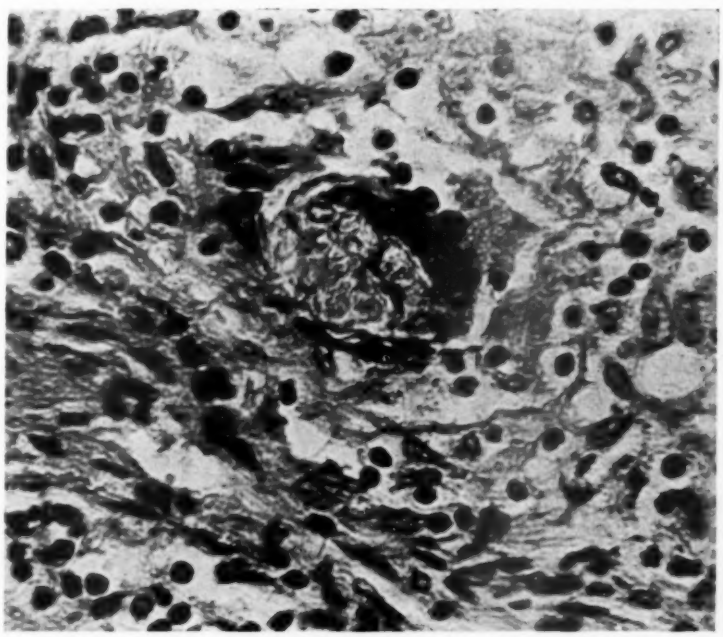

Fig. 9.—Photomicrograph, 600×, showing laminated bodies in cytoplasm of giant cell in lymphnode. The inclusions are lighter staining than the cytoplasm.

and macrophages were present about many lesions in the lungs. Other presumably older lesions were closely invested by layered collagenous connective tissue. The cytoplasm of many giant cells contained vacuoles in which there was eosin-staining material resembling poorly formed asteroids. Many giant cells contained inclusions, some of which were crystalline; others were calcified and laminated like those described by Schaumann (Fig. 9). In the myocardium, lesions extended from epicardium to endocardium; they were more irregular and lacking the sharp collagenous delineation noted in the lungs. The earliest lesions consisted of two or three epithelioid cells and a scattering of lymphocytes adjacent to a small blood vessel. The oldest lesions were moderately fibrotic. They interrupted the myocardial fibers, many of which had completely disappeared within the tubercles (Figs. 7, 8). In the lungs, there was associated thickening of the

septal walls, chronic obliterative endarteritis of bronchial vessels, and red cells and hemosiderin in the alveolar spaces. In the spleen, the largest lesions occurred within the Malpighian bodies. The lymph nodes were extensively replaced by discrete lesions, many of which were rounded and wrapped in collagen, presenting a layered, onionskin appearance. In the large tracheobronchial nodes, there were broad, hyaline scars in which only a few isolated epithelioid cells and giant cells remained. In the larger nodes there was granulomatous involvement of the capsular and pericapsular tissue. In the liver, the granulomata had irregular edges like those in the myocardium. Most of them occurred in the portal triads, but an occasional small mid-zonal lesion was found. There was mild to moderate proliferation of portal fibrous tissue, infiltrated by lymphocytes, plasma cells, and polymorphonuclear leucocytes, occasionally accompanied by marked bile duct proliferation. Some of the scarification, if not all, appeared to be due to the healing of previous sarcoid granulomata. The central areas were the site of congestion, hemorrhage, and, frequently, necrosis. Several small granulomata occurred within the parenchyma of the pancreas. No granulomata were found in the kidneys. Numerous renal tubules were necrotic and calcified. A small tubercle was found in the thyroid. None were found in the bone marrow. Acid fast stains for tubercle bacilli were negative.

COMMENT

Myocardial sarcoidosis is a lethal lesion, death having been attributed to it in nine of the thirteen reported autopsied cases. This case is believed to be that of the first white man known to have died of myocardial sarcoidosis, the eight previous cases having occurred in Negroes, five of them being young men. It also differed from previous cases in that the course was that of chronic congestive heart failure. In the two reported autopsied cases of heart failure due to left ventricular insufficiency, the failure was acute, lasting ten weeks[5] and four weeks,[7] respectively. The five cases of sudden death due to sarcoidosis with myocardial involvement were probably attributable to ventricular fibrillation or Stokes-Adams syndrome. Cor pulmonale due to sarcoid of the lung is common and invariably complicates the rarer congestive failure due to myocardial sarcoid. It was also present in this case, but it was clinically subordinate. Paroxysmal arrhythmia and defects in the conduction system are the most common clinical manifestations of myocardial sarcoid.[2,3,5,6,7,10,11]

The nonspecific changes of diffuse myocardial damage indicated by the electrocardiogram during life in this case corresponded to the extensive infiltration of the myocardium present at autopsy. The appearance of auricular flutter as a terminal event and the persistent first-degree auriculoventricular block corresponded to the functional abnormalities of the previously described cases. It was suggested by Bates[8] that unexplained tachycardia in known cases of Boeck's sarcoid pointed to the presence of myocardial involvement. In the case reported here, in spite of extensive myocardial involvement, the heart rate did not become rapid until the terminal episode, and it never was out of proportion to the degree of heart failure.

The diagnosis of sercoidosis should not be made without considerable circumspection and the marshalling of all available facts. Nickerson[4] has enumerated several histologic criteria which have been embellished by Bates.[8] They are: (1) no caseation, (2) no caseating tuberculosis elsewhere, (3) reticulum fibers present, (4) no polymorphonuclear leucocytes, (5) large giant cells with many nuclei, (6) lesions in the portal triads, (7) no carbon in extrapulmonary

lesions, and (8) presence of giant cell inclusions. These criteria have been fulfilled in the case described here. A further criterion suggested is a strong tendency toward discreteness and laminated, hyalinized envelopes in the presence of older lesions.

Definite fibrosis of organs occurred as a result of the healing of sarcoid granulomata. In the lung, alveolar septa and peritruncal fibrous tissue became thickened. In the spleen, thickening of the septa occurred. In the liver, there was a conspicuous increase in the portal fibrous tissue. Sarcoid is therefore postulated as a rare cause of cirrhosis.

SUMMARY

The first case of death due to myocardial sarcoid in a white man is reported, the eight previous cases having occurred in Negroes. This case also differs from the preceding cases in that the lesion had produced myocardial insufficiency with chronic congestive heart failure, as well as cor pulmonale. Evidence is presented that the lesions in the liver may be a rare cause of cirrhosis.

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Review of Meeting

REVIEW

First International Congress of Cardiology, Paris, 1950

Part II

Demetrio Sodi-Pallares, M.D., and Jorge Espino-Vela, M.D.

Mexico, D.F.

PHYSIOLOGY

1. The functional refractory period was studied[75] in the auricle and the ventricle of mammals. Reference was made to the work of Lucas who showed in the turtle's ventricle that using two pairs of stimuli (conditioning and test) and applying the second one within a certain limit of time after the first one produces a response preceded by a latent period. This period depends on the moment when the second stimulus is applied, but the interval between the responses to both stimuli is always constant. (Functional refractory period is different from the absolute refractory period since the latter is determined by the interval between two excitations.) It was thus proved that the auricle and ventricle of mammals have this property.

2. The general effects of total interruption of circulation by the clamping of both venae cavae were studied in forty dogs[76] with or without perfusion of the cephalic end of the carotid arteries. All animals not subject to perfusion died between ten and fifteen minutes after the clamping. The perfused animals lived because blood was carried to the nervous centers and to the coronary arteries. The greatest life span under such circumstances was thirty-eight minutes. Electrocardiographic and electroencephalographic tracings were taken before, during, and after the experiment. They were studied after careful analysis. The possibility of access to the heart without circulating blood in both ventricles was explored.

3. The influence of the vagus and of the sympathetic nerves[77] on the coronary circulation was studied, using the Heymans-Kochman perfused heart preparation. Stimulation of the vagus increased the coronary flow the same as with the injection of acetylcholine. This was due to a vasodilating action. Stimulation of the sympathetic nerves or injection of Adrenalin diminished the flow in the beginning, especially when the inotropic positive effect was weak, that is, they were vasoconstrictors; on the other hand, there was increased flow

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parallel to the increase of ventricular contraction. Therefore, coronary vessels do not differ from other vessels in the body as far as innervation and vasomotor actions are concerned.

4. The influence of extravascular factors on coronary circulation was studied in the heart by perfusion.[78] Increase of diastolic pressure with increase of right or left ventricular contractions increased the total coronary flow as well as that of the coronary sinus. This fact was attributed to metabolite accumulation due to overactivity. Compression of the coronary vessels during systole favors coronary circulation. If the venous flow instead of the arterial flow was registered, it was seen that it increased during systole and decreased during diastole. Coronary blood flow increased in ventricular fibrillation with low arterial pressure (less than 60 mm. Hg), and it decreased invariably if pressure was above 80 mm. Hg.

5. The mechanism of the production of hypervolemia and edema was studied[79] in heart failure. It was thought that decreased circulation time determined an increase of CO_2 in the venous blood with sodium retention; this gave rise to an increase of the total ion content causing water retention in the extracellular spaces and, consequently, edema and hypervolemia. To prove this, dogs were injected daily with bicarbonate solution, and they were made to breathe alternately 10 per cent oxygen and CO_2. While breathing CO_2, diuresis and sodium elimination decreased.

6. Experimental arteritis produced by aseptic or septic emboli was studied.[80] At the same time several other experiments were undertaken: (1) By treating guinea pigs with repeated injections of heterogeneous sera of the horse or ox, pericarditis, arteritis, and glomerulonephritis resulted. (2) By treating animals with high doses of desoxycorticosterone acetate, lesions corresponding to periarteritis nodosa, arteriolar necrosis, and telangiectatic arterial lesions were produced. (3) By subjecting animals to different intoxications, lesions of endarteritis, hypertrophic sclerotic panarteritis, and arteriolar necrosis resulted. (4) By combining these experiments an aggravation or summation of these lesions was obtained.

7. The subject of isolated pulmonary hypertension[81] was discussed. Diagnosis through catheterization was extremely difficult, since it is not enough to find merely pulmonary hypertension. It might be a case of patency of the ductus with pulmonary hypertension or interauricular septal defect with inverted shunt. A case was presented of isolated pulmonary hypertension confirmed by autopsy which was diagnosed as a double mitral lesion and tricuspid regurgitation. Tricuspid regurgitation was functional in nature, due to dilatation of the right cavities. Two more cases were presented where the diagnosis of pulmonary hypertension was made after eliminating any septal defects through catheterization and angiocardiography.

8. A study of venous pressure[82] in the limbs was done with reference to a given level: that of the collapsed subclavian vein referred to the suprasternal notch for the arm or an "O" abdominal level for the leg. Levels obtained were 11 mm. for the arm and 25 mm. for the leg. Theoretical arguments for

the proximity of the levels were discussed as well as the role of juxtathoracic venous collapse. The causes tending to separate these levels and the mechansim of the tests of Valsalva and Müller were also discussed.

ELECTROCARDIOGRAPHY

Clinical Electrocardiography

1. The case reports of two sisters, 24 and 34 years of age, with familial congenital bradycardia due to complete atrioventricular dissociation, were presented.[83] There was no history of rheumatic fever, congenital syphilis, or diphtheria. It was known that bradycardia in one of them had been present since the age of 2 years. Three brothers had died when they were children. In the elder sister a marked ventricular acceleration was registered after the injection of 1 mg. of atropine. The interest of this paper lies in several facts. Both cases fill the requirements set by Yater: auricular rhythm acceleration provoked by ventricular systoles and greater acceleration of the ventricular rhythm provoked by atropine. These cases are the fourth instance of congenital familial block in the literature.

2. Fifteen crises of paroxysmal tachycardia[84] were studied in a patient with permanent Wolff-Parkinson-White syndrome. Auricular premature beats frequently appeared, and when late in diastole they were followed by the Wolff-Parkinson-White type of ventricular complexes. If they appeared early, they were either blocked or were followed after an interval longer than normal by a crisis of paroxysmal tachycardia. All crises of auricular tachycardia were started by precocious auricular premature beats. It was argued that the excitation passed from the auricles to the ventricles by an anomalous path. An early auricular premature beat found the bundle of His in a refractory stage and it was blocked. Occasionally, the excitation wave was conducted although delayed by the normal pathway, and it finally found the bundle of His in an excitable phase after going through the ventricle. It reached the bundle in a retrograde fashion to the auricles, which started a new sinus excitation and the circuit of stimulations was started. This was held to account for the paroxysmal tachycardia.

3. One hundred normal electrocardiograms[85] were studied in which the voltage in V_5 and V_6 was equal to or greater than 2.6 mv. or where the sum of R in V_5 and V_6 and S in V_1 and V_2 was more than 3.5 mv. Seventy per cent were found in subjects with etiological factors capable of producing left ventricular hypertrophy. The study of another 100 normal electrocardiograms with lower voltages than were previously mentioned and of fifty typical electrocardiograms of left ventricular hypertrophy allowed the inference that such numerical patterns are of great value (although not absolute) in the early diagnosis of left ventricular hypertrophy.

4. A summary of electrocardiographic findings[86] was presented from fifty-two uremic patients with malignant hypertension, subacute or chronic glomerulonephritis, and, in a few cases, with congenital renal malformations. In 25 per cent of the patients the changes were similar to those described in hyper-

potassemia (high and peaked T waves, flattened P waves, sinoauricular blocks, intraventricular conduction disorders, auricular and ventricular standstill, or ventricular fibrillation). A correlation could not be established between the electrocardiographic changes and the potassium levels in the blood; this suggested the possible influence of other metabolic factors.

5. A study of the electrocardiographic findings[87] during gall bladder colic produced by handling of the biliary passages during surgical interventions or due to injection of saline solution under pressure was presented. The study was made in normal patients, in some with coronary disease, and during different surgical operations (gastrectomies, abdominal hernias, and so forth). Several conclusions were reached as regards cholecystocoronary relations and changes observed during the pain.

6. The electrocardiograms[88] in fifty-two patients with typhoid fever were studied, and the main changes observed were sinus tachycardia, auriculoventricular block of first degree, and changes in voltage of the T wave. These all disappeared when the clinical course improved or on the administration of vitamin B_1, nicotinic acid, or potassium chloride. In one patient who was examined at autopsy there were microscopic changes in the myocardium. In another case there were edema of the pericardium and the endocardium and round-cell infiltration between the muscular fibers and around the vessels without formation of clumps. There were no degenerative lesions of the muscle fibers.

7. The electrocardiograms of 115 normal pregnant women were studied,[89] and the results were compared with those obtained after delivery. Q_3 was almost always small. It was due in the majority of the patients to a vertical heart and was a consequence of the presence of a Q wave in aV_F; in other instances ("horizontal hearts") the Q wave was given by an initial positivity in aV_L associated with a small Q wave in aV_F. In the majority of the cases the Q wave persisted after delivery. AQRS, generally speaking, deviated to the left. The ventricular gradient remained normal in its relations with AQRS. Inversion of T in Lead III was rare, and its relation to the inversion of T in aV_F was still rarer. After pregnancy T became positive.

8. An electrocardiographic study was done in an anencephalic monster[90] twelve hours after birth. Sinoauricular block and supraventricular extrasystoles were detected. There was marked bradycardia as the monster was dying. The experiments on animals submitted to cold and the cases of death due to cold were reviewed. Pictures of the monster were presented and the cardiac rhythmic disturbances were discussed.

9. The electrocardiographic changes in fifty patients with general toxicosis[91] were reported. Inverted T wave was found in 82 per cent of the cases. Lengthening of the Q-T interval was found in 57 per cent and, less frequently, a decrease in the voltage of QRS. The changes were similar to those found in other childhood diseases (malnutrition syndromes, typhoid fever, nephritis, and so forth), for which reason it was believed that lack of some principal substances, especially vitamin B_1, nicotinic acid, and potassium salts, was responsible for such changes. These changes were reversible with return to normal health.

10. The electrocardiograms of forty-eight patients with aortic stenosis[92] were discussed. In every case of calcified aortic stenosis, complete or incomplete bundle branch block was found. Of fourteen patients twelve had left block and two had right block. In five patients with syphilitic aortitis with a double lesion, four showed left block, complete or incomplete, and one had right block. Among twenty-five rheumatic patients and three with congenital heart disease (noncalcified aortic stenosis) there were two with left blocks and three with right blocks. Generally speaking, all the tracings were suggestive of left ventricular hypertrophy. The position of ÂQRS and the index of Lewis were normal when ventricular hypertrophy was of the concentric type and were modified when the ventricular cavity underwent dilatation. There were often auriculoventricular blocks that might have been caused by digitalis which was given in almost every case.

11. A case of sinus arrhythmia with displacement of the pacemaker was studied.[93] At the same time the presence of a parasystole was admitted with a center of stimulation in the same sinus node. The basal rhythm and the pararhythm showed almost the same degree of frequency. The period of the latter was not apparent because the premature beats were produced in an isolated fashion, but a maximal common divisor was found, and it could be shown that the period was equal to that of the basic rhythm. Displacement of the pacemaker in the course of this disorder was obvious. It took place along the sinoauricular portion, and it was located at the sinocoronary focus.

12. The authors attempted to prove that in cases of angina pectoris[94] not all who show increased voltage of the T wave in left precordial leads have subendocardial ischemia. They based their statements on several observations: (1) Many patients developed typical posterior infarction. (2) During the crises, significant changes were not seen in V_L. (3) There may be changes over the scapular leads exploring the posterior epicardium with no changes in V_R. For such reasons it was concluded that the changes described may belong to posterior and not subendocardial ischemia.

13. A clinical and electrocardiographic study[95] was undertaken in 320 cases of myocardial infarction. Groups with and without shock were described: digestive groups, painful and painless groups, and so forth. Aneurysmal, embolic, and thrombotic complications and the influence of anticoagulant therapy were also dealt with. Clinical symptoms and electrocardiographic signs were compared showing a lack of parallelism at times. Electrocardiographic locations were also compared with autopsy reports.

14. Venous coronary insufficiency due to stasis,[96] experimental coagulation, and thrombosis in dogs was expressed in electrocardiographic injury and ischemia patterns. The following types were described: (a) slow and late appearance, (b) those lasting several hours, (c) complete regression without necrosis, and (d) discordant or concordant development of injury and ischemia. Injection of streptococci cultures in the pericardial sac produced coronary thrombophlebitis. A new clinical entity was described to be distinguished from infarction and pericarditis.

15. M complexes in V_1 and V_2 were studied[97] in eight patients with rheumatic carditis. In every case an increased sedimentation rate, leucocytosis, and fever were present. M complexes always disappeared in V_1 and V_2 after antirheumatic treatment. For this reason they may constitute a valuable sign of rheumatic carditis.

16. A permanent nodal rhythm was described[98] in a 39-year-old individual with a syphilitic history. The rhythm was not changed after antisyphilitic treatment or after gastrectomy for gastric ulcer. Administration of 1 mg. of Adrenalin was followed by sinus rhythm despite slowing of frequency. The action of Adrenalin was discussed.

17. The systolodiastolic constant of Lian[99] was studied in the electrocardiograms of pregnant women, and it was found that 26.3 per cent of the subjects showed a constant above 0.0049. Comparative studies were made between the values of the constant and blood calcium content.

Experimental Electrocardiography

1. The electrocardiographic changes[100,101] produced by the administration of potassium salts were studied in normal subjects and in patients with cardiac disease. The changes were especially seen in Leads I and II.[100] In these leads the RS-T tended to go up if the potassium level was low, and the T wave became narrower, tall, and peaked. Sometimes its direction turned from negative to positive. QT variations might also be observed, as well as variations in the morphology of QRS.[101] There was no direct relationship between the electrocardiographic changes and the level of potassium in the blood stream.[100] It was felt that potassium acts directly on the myocardial fibers and favors the synthesis of lactic acid which would cause the increase in amplitude of the T wave.

2. The diagnostic importance[102] of the modifications produced in the ventricular complex through stimulation of the carotid sinus was studied. In normal subjects the changes were slight, and the modifications in amplitude of the T wave did not exceed 1 mm. Instead, cardiac patients showed notable changes of T, with marked diminution of voltage and inversions of the same wave in leads where it is normally positive. There were T waves of normal polarity, and they changed frequently in their polarity after stimulation. Quite similar morphological changes were observed in the tracing after the intravenous injection of acetylcholine.[103] There were frequently prolonged cardiac standstills, and in one case auricular fibrillation occurred.

3. The electrocardiographic modifications[104] produced by emotional conditions were studied both under normal and pathological conditions (particularly in cases of coronary insufficiency). The clinical importance of these data was stressed.

4. The electrocardiographic changes produced in the dog's heart by the handling of the heart that takes place before experimental coronary occlusion were reviewed.[105] These changes were considered as "technical artifacts." The changes on the ventriculogram produced by the opening of the chest and the pericardium were mainly in the T wave. It became flattened or inverted in

75 per cent of the cases. Changes of the QRS complex depended mainly on the position of the heart on opening the chest. Anesthesia with 10 per cent Nembutal solution frequently produced bifid, diphasic, and even inverted T waves. Various rhythmic disturbances were frequently found, such as blocks, and in two patients who were anesthetized, ventricular fibrillation was observed.

5. The action of dihydroergotamine 45 (DHE45) was tried on experimental coronary occlusion in the dog's heart.[106] The action of the drug on ischemia and injury patterns was variable. The tracing might not be modified, or the electrocardiographic changes might increase or diminish. The drug did not prevent or modify ventricular fibrillation, nor did it modify auriculoventricular block. It was believed the drug had a mixed action in which it was well to emphasize its adrenolytic and sympathicolytic effects as well as its direct action on the muscle fiber. According to the predominance of each of these actions, progression or regression of the patterns of ischemia or injury would be observed.

6. In three papers[107,108,109] the electrocardiographic changes produced by experimental pulmonary embolism or in acute cor pulmonale produced mechanically through compression of the pulmonary artery were studied. In one[107] it was pointed out that a positive displacement of the RS-T segment takes place in the right ventricular epicardial surface and a negative displacement of this segment in the left ventricle. This change referred to the acute ventricular dilatation which caused the superficial muscular layers of the right ventricle to shrink and receive less oxygen. In another paper[108] an RS-T positive displacement at the epicardial surface of the pulmonary conus, the trabecular zone, and the right cavities was described; this suggested a lesion in the right aspect of the septum. A Q wave was also found in the epicardial surface of the pulmonary conus. Also, rsR complexes (mirror image of the epicardial surface of the conus) were found in the ventricular cavities. Finally, coronary T waves and negative displacement of the RS-T segments were found in the left ventricle. Many of these changes were produced by an inverted Bernheim syndrome with intraseptal block.

7. The sinoauriculo-nodal junction was studied in the frog's heart.[110] The heart was washed and perfused. It was then opened, placed in extension, and cinemicrophotographs were taken. By this method, sinus blocks, sinoauricular blocks without sinonodal block, nodal rhythms, intra-auricular blocks, auricular fibrillation, and other disorders were studied.

8. The process of septal activation was studied[111] in the dog's heart, and it was found that the mean general direction of septal activation developed from above downward; the first regions of the right septal surface activated were those proximal to the anterior papillary muscle. In the left surface, it was the region located halfway between the base and the apex. The greatest part of the septum belonged to the left ventricle, and it was activated by the left branch of the bundle of His. Muscular tissue, behaving electrically as the left ventricle, approached the right aspect of the septum, and there were areas of the same surface that behaved as the left ventricle. The activation wave swiftly crossed those portions (around 0.01 second), for which reason it is not admissible that the greater duration of QRS in patients with bundle branch block should be due to the fact that

the activation wave crosses the septum in 0.04 or 0.05 second. Everything led to the belief that delay in bundle branch block took place in the thickness of the septum, although in a circumscribed area (1 or 2 mm.) and quite close to the right septal surface.

9. Experiments on cadavers[112] were undertaken to study the electric field produced by an artificial dipole located within the human chest. The tracings obtained were analyzed from leads as described by Sulzer and Duchosal. The direction of the artificial dipoles was compared with that obtained by these leads before and after a corrective factor which considered the distances between the electrodes. Great differences were found between the directions of the true doublets and the ones calculated. These differences were discussed and were attributed by the authors to lack of uniformity of the conducting medium.

10. The electrocardiographic modifications produced by precordial cooling[113] were studied. In five normal subjects there was an evident decrease of the T-wave voltage in precordial leads. In five more subjects with left pneumothorax and in two with cardiac enlargement, congestive heart failure, and huge emphysematous vesicles there was no change. In seven out of eight patients with cardiac disease, there were evident changes, whereas cooling of the abdominal region and immersion of one hand in ice cold water produced no change. In several cases inversion or flattening of the T wave disappeared with amyl nitrite or with aminophylline. It is believed that epicardial cooling produces an angiospastic reflex.

INTRAVENTRICULAR POTENTIAL

This was one of the subjects most studied in the experimental field, and it included the catheterization of the left and the right cavities. The experimental aspects in animals and the clinical viewpoint were both covered.

1. By means of right intra-auricular leads in the dog's heart, the process of auricular recuperation was studied after the myocardium had been injured with alcohol and silver nitrate injections.[114] In cases of auricular fibrillation[115] it was shown that a regular undulatory cycle was present, with periods of 0.14 minutes, in almost every case. The authors thought that this reinforced the hypothesis of circus movement in this rhythmic disturbance. Since the contact with the exploring electrode may start a transient auricular fibrillation, this led to the belief that a partial refractory period may be the cause of the circus movement. In the experimental aspects, the morphology of the delta wave in the Wolff-Parkinson-White type of premature beats was studied using the same type of right intra-auricular leads when these beats were produced by stimulation of the upper portion of the interventricular septum.

2. Right intra-auricular potential in human hearts in patients with right ventricular hypertrophy[116] gave qR and qRs type complexes. In right bundle branch block[117] the tracings were of the RSrS′, QrsR, rSr′, and rSrS′ types; this depended on the position of the exploring electrode in the auricular cavity. It is well to mention that in this type of block there are always two positivities, which distinguishes these cases from those due to ventricular hypertrophy.

3. In right intraventricular potential of human hearts, right hypertrophy[116] gave rS type complexes with high voltage, but two positivities were not to be found. On the contrary, in right bundle branch block[117,118] the types encountered were rsR′S′ or rsr′S, proving again the existence of two positivities.

4. The left cavities of the human heart were also explored,[119,120] and it was demonstrated that the morphology of P, as was expected according to the theory of the dipole, is of the RS type[119] with a predominance of positivity or negativity according to the location of the exploring electrode.

5. In the left ventricular cavity there were normally only negative complexes[120] of the QS type, although some authors[119] also found tracings of the QRS, qRS, and RS types. (We believe these last types were the consequence of a certain degree of injury produced by the exploring electrode, since they were always followed by marked displacements of the RS-T segment.) In patients with left bundle branch block the intraventricular tracings were of the RS or Rs type[119,120] with a slurring of the initial portion of R[119] quite similar to that described in Wolff-Parkinson-White syndrome. Many patients were considered clinically as having left ventricular hypertrophy; actually they had incomplete blocks of the left branch of the bundle of His[120] as proved by the inscription of the initial positivity of the left ventricular cavity.

CONSIDERATIONS ON DIFFERENT TYPES OF LEADS

1. V_E, V_{5D}, and V_{ASD} leads (in the upper right abdominal region)[121] proved useful in identifying right ventricular hypertrophy and slight degrees of incomplete right bundle branch block. Generally speaking, however, the tracings were similar to those taken from V_1 and V_2.

2. A bipolar thoracic lead was proposed, which was genuinely bipolar,[122] and was obtained by leading from the two points of maximal potential at the right and left sides of the precordium. It was proposed that this lead be called the "third precordial." It merely closes the circuit of two precordial leads. In normal subjects[122] it has the morphology of a normal electrocardiogram with absence of Q and S waves. P is positive or diphasic and T is positive. The morphology of this lead is not modified by variations of anatomical or electrical position of the heart. In myocardial infarction or in coronary alterations[123] the "third precordial" lead is considerably modified. If the alterations are in the left ventricle, the potential of R increases, and there is a negative displacement of RS-T and inversion of T. If the changes are in the right ventricle, a great Q wave appears, the voltage of R increases, RS-T is displaced upward, and the T wave is positive. (We believe that the modifications in this lead may be inferred, knowing the unipolars which form the lead. On the other hand, to recognize the origin of the alterations of distant bipolar leads without the registration of the corresponding unipolars is quite difficult.)

3. The posterior aspect of the heart[124] was studied by means of dorsal and unipolar esophageal leads. In the horizontal heart the esophageal low tracing was of the RS type, whereas in the vertical heart the low esophageal tracing was of the qRs type. There was an interchange of anterior morphology if, to

the position described, a clockwise rotation is added on the longitudinal axis. The right dorsal leads were normally of the QR type. This is important since a delayed intrinsic deflection in these points does not imply a disturbance of the intraventricular conduction. In pulmonary emphysema all esophageal and dorsal leads were of the QS type, but in left ventricular hypertrophy they were of the qRs type. Quite often in arteriosclerotic heart disease, during a crisis of angina, and especially in high posterior myocardial infarction, electrocardiographic changes were only present in esophageal leads.

4. The comparative clinical value[125] of classical and unipolar limb leads was studied, using the method of Goldberger, as well as the variations of both as regards the electrical axis. It was concluded that both types of leads have the same value. (We believe this was to be expected, since the interrelation of the two types of leads is well known. On the other hand, the differences that depend upon the thoracic constitution of the different resistances between the electrodes and the skin and the central terminal employed are of more theoretical than practical importance up to the present time, even though there are some exceptions.)

5. The comparative clinical value[126] of the CF and V leads was studied, and it was found that in 85 per cent of the cases (50 normal subjects and 546 cardiac patients) both types of leads were practically equal. The differences dependent upon the position of the electrical axes were also studied. It was shown that in several heart ailments there might be negative T waves in $CF_{2,5,6}$ whereas the same deflection was positive in the V leads. In patients with myocardial infarction, during the late stages of the disease, the T wave remained negative in $CF_{1,2,5,6}$ while in the corresponding V leads it became positive. (We believe one must not forget that CF leads are bipolar and are less similar than V leads to the tracings taken from the epicardial surface of the heart. It is possible that a greater number of cardiac diseases might be recognized using the CF leads, but it is also true that with the same leads one may erroneously diagnose heart disease or the type of lesion may be misinterpreted.)

MEDICAL AND SURGICAL THERAPY

1. Forty cases of pulmonary stenosis with surgical treatment[127] were reviewed. The importance of preoperative angiocardiography and also of cardiac catheterization and retrograde aortography was stressed. The latter was more important postoperatively. The most common difficulties of technique and postoperative complications and their solution were discussed. Experimental work was reported in an attempt to solve these problems in the most physiological way.

2. A clinical, radiological, electrocardiographic, and phonocardiographic study was done on a group of patients who had undergone surgical treatment of mitral stenosis.[128] The different methods used at the present time were judged: (a) valvulotomy with Bailey's technique, (b) Bland-Sweet operation, consisting of the anastomosis of the azygos vein with the upper branch of the inferior pulmonary vein, (c) Blalock's operation, producing an interauricular septal defect, and (d) Rappaport's operation, producing a union between the left

auricular appendage and the left ventricle by means of an arterial graft. The selection and preparation of the patients and the clinical and electrocardiographic modifications observed following surgery were discussed. Common operative and postoperative complications were also referred to.

3. One hundred patients with congenital heart disease who were operated on[129] were reviewed. Of forty-seven with patency of the ductus, three died of syncope or heart failure, and two developed recanalization but were reoperated upon successfully (these had been ligated with one ligature and not doubly ligated). Of forty-seven patients with tetralogy of Fallot, twelve died; death was due mostly to operative or postoperative anoxia of anesthetic origin. The remaining thirty-four were living and their improvement on the average had been considerable. Of four patients operated on for coarctation of the aorta, two died in heart failure. Another patient died without regaining consciousness from anesthesia. The last patient is living and well. Four patients with transposition of the great vessels were unsuccessfully operated upon for anastomosis of the subclavian and the pulmonary arteries.

4. Another fifty patients with cardiovascular malformations[130] who were operated on were reviewed. Patency of the ductus, tetralogy of Fallot, pulmonary atresia, supernumerary venae cavae, pericardial malformations, superior vena cava aneurysms, coaractation of the aorta, and so forth form this group. Results were summarized in comparative statistics.

5. Ninety patients with protracted heart failure[131] and seventeen who underwent surgical ligation of the inferior vena cava[132] were reviewed. The different surgical techniques, operative mortality and its causes and immediate and late effects up to three years follow-up, and indications and contraindications were discussed. Comments on the pathogenesis of the physiological modifications due to ligation of the vessel were reported.

6. Ligation of smaller pelvic veins and veins of the lower extremities and even of the upper limbs was done[133] for the purpose of obtaining similar effects to those of ligation of the inferior vena cava for the treatment of heart failure. Twelve patients were operated on in whom medical treatment had been ineffective. Eight patients had mitral stenosis, three had hypertension, and one had cardioangiosclerosis. In two patients the internal iliac vein on one side and the external iliac vein on the other were ligated. In nine patients both external iliacs were tied, and in one patient the common femoral vein on one side and the external iliac vein on the other were ligated. The principal sequela to be watched for is hypotension following the ligation in hypertensives. This risk is reduced by a two-stage operation. All but two patients improved; all had lowered venous pressures, and 70 per cent exhibited diminution of heart size on the roentgenogram.

7. End results of pericardiotomy[135] in cases of chronic constrictive pericarditis were analyzed. The authors studied the main pathological changes of chronic constrictive pericarditis. They described the anatomical and physiological changes which resulted. The data gave the basis for operative indications, and the Schmiedem type of pericardectomy was used. Surgical technique and results in the cases were briefly discussed.

8. From the plants of the thevetia species (*Thevetia gaumeri*)[136] a substance has been isolated called tevetoidina. This new glycoside melts in a shut container at 210° C. Its molecular weight is 710. It is a crystal in the tricyclic system. An alcoholic solution gives a deep violet color when concentrated and sulfuric acid is added. Structural analysis reveals the presence of digitoxigenin, tevetose, glucose, and acetic acid. In the frog's isolated heart it produced systolic arrest in concentrations of 4×10^{-5}. The smallest (minimal) lethal dose (L.D. 50) for the frog, obtained by the method of Behrens, was 0.067 mg. per gram of body weight. Tevetoidina reduced experimental heart failure in the cardiopulmonary preparation of Starling at the dose of 0.8 to 1 mg. A complete effect was reached in a few minutes with a drop of pressure in the right auricle, the left auricle, and the pulmonary artery. Increase of the cardiac output followed. Similar results were obtained with 0.08 to 1.0 mg. of ouabain. Its action was fleeting, and cardiac failure occurred forty to fifty minutes later. In dogs toxic effects were reached with doses of 0.5 to 0.6 mg. per kilogram, and they consisted of a prolonged P-R interval followed by atrioventricular dissociation and multifocal extrasystoles. The P-R interval returned to normal in one hour.

9. The action of tevetoidina[140] was also studied in human heart failure. A group of patients were selected for that purpose who had not been given digitalis. The changes in pulse, auricular fibrillation, venous and arterial pressures, and the action on the effectiveness of cardiac contraction were studied. Electrocardiographic changes denoting myocardial impregnation and intoxication were analyzed. The speed at which favorable effects appeared and the rate of excretion of the drug were studied. Results obtained were comparable to those of digitalis and ouabain. Clinical applications were discussed especially concerning acute myocardial failure and a comparison with digitalis therapy.

10. It was investigated through experimental studies in dogs[137] to what extent the right auricular appendage retains foreign bodies present in the circulating blood. The anatomical structure and hemodynamic conditions help to retain such foreign bodies.

11. In order to determine the therapeutic value of oxygen therapy[138] in different circulatory disturbances (congestive heart failure, myocardial infarction, and so forth) oxygen consumption was studied by having patients breathe mixtures of this gas. Results were compared with those obtained in normal subjects.

12. The function of the supracardiac paraganglia was studied.[139] Intra-aortic lobeline was used, and it was shown that injection in the aortic arch produced reflex hypertension of higher degree than that obtained by injection at the base of the aorta. If the nutritional artery to the superior paraganglion be destroyed, the reflexes were suppressed. On the contrary, extensive destruction of the aortic adventitia did not influence the reflex. It was inferred that the origin of these reflexes is in the superior paraganglion.

13. The effect on liver function in patients treated with Dicumarol[141] was studied. This study was undertaken due to the fact that a patient with mitral and tricuspid valvular lesions had been prescribed Dicumarol for multiple

emboli. He showed yellow pigmentation of the skin and mucosae during this treatment. Liver function was thus studied in forty-four patients who received Dicumarol treatment on the average for over six months. They comprised patients with coronary occlusion or thrombotic arteriosclerosis. In every case the Van den Bergh, bromsulfalein, total and esterified cholesterol, plasma globulin and albumin, cephalin cholesterol, and thymol tests were done. It was concluded that Dicumarol does not alter the functions of the liver when given in therapeutic doses even for long periods.

14. Electrocardiographic studies were made after anesthesia of the lower cervical ganglion and of the vagi.[142] This was done because anesthesia of the stellate ganglion of the lower cervical sympathetic nerve and of the vagi at the base of the neck has gained prominence in diagnosis and therapy.

15. The effects of "prolonged" oxygen therapy[143] were studied. Oxygen was administered by inhalation to several patients with recent and chronic myocardial infarctions. It was found that the electrocardiogram taken during oxygen inhalation rendered the T wave positive. In patients with acute and chronic myocardial infarctions, improvement was evident clinically and electrocardiographically. Without having standard measures as yet, it was recommended that oxygen be inhaled three times daily for twenty minutes "during four to six months continually." In other patients without myocardial infarction it was seen that oxygen made a first-degree atrioventricular block disappear in a case of cardiosclerosis and also a right bundle branch block in a similar case.

16. It was demonstrated that acetyl-beta-methylcholine[144] may impregnate the myocardium by the method of iontophoresis. Using featherless chickens the following experiments were carried out. Ionizations with potassium cyanide were done, and this caused the death of the animal in twelve to sixteen minutes. In this process the potassium ion and the cyanide ion dissociate. The latter is responsible for the animal's death. Ionizations with vomicine were also practiced which killed these animals in fourteen to eighteen minutes with symptoms of strychnine poisoning. In order to study the first of the substances mentioned, a reagent was found whose reaction was invariably characteristic in the presence of the drug. The reagent was not toxic when given intramuscularly or by vein, but if, after being used, the reagent was ionized, the animal died immediately. The presence of the drug was identified in the cardiac muscle after iontophoresis.

17. A paper was read dealing with the search for and prophylaxis[145] of heart disease in tuberculosis surveys. A three-year experience of the author showed: (1) that routine examination of the chest leads to detection of a high number of heart cases (5.3 per cent) even though the method is intended primarily to discover pulmonary lesions; (2) that tuberculosis surveys receive a number of patients who feel that they are tuberculous and in reality have cardiac or cardiovascular disease; (3) that pulmonary diseases affect the heart.

18. Different types of heart disease[146] were studied in nearly 8,000 Jews in a Jewish hospital in Buenos Aires. The largest incidence was that of hypertension (68.5 per cent), followed by coronary disease without hypertension (11.7 per cent); rheumatic heart disease came third with 11 per cent; cor pul-

monale was fourth (2.3 per cent); then came in order thyroid heart disease (2.2 per cent), congenital heart disease (1.2 per cent), cardiovascular syphilis (0.5 per cent), bacterial endocarditis (0.4 per cent), and finally a mixed group usually of unknown cause (2.1 per cent). The high proportion of hypertension among Jews, similar to that of the Negroes in the South of the United States, might be accounted for by the same emotional factors related to their history. The rarity of cardiovascular syphilis might be explained by some customs observed by them, among which are circumcision and marriage during adolescence.

PAPERS SUMMARIZED

75. Méndez, R., Mandoki, J. J., and Méndez, C.: El período refractario funcional de la orejuela y del ventrículo de mamífero, Inst. Nac. de Card. México.
76. Parianex, I., and Berreta, J. A.: La interrupción de la circulación con o sin perfusion de las coronarias y el encéfalo, Argentina.
77. Rosenblueth, A., García Ramos, J., Luco, J., and Alanís, J.: La influencia del vago y del simpático sobre la circulación coronaria, Inst. Nac. de Card. México.
78. Rosenblueth, A., García Ramos, J., and Alanís, J.: La influencia de los factores extravasculares sobre la circulación coronariana, Inst. Nac. de Card. México.
79. Siveir, F., Suarez, F., Burbano, A., and Bravo, J.: Contribución experimental al conocimiento del mecanismo de producción de la hipervolemia y de los edemas en la insuficiencia circulatoria, Zaragoza, España.
80. Mosinguer, M.: Estudios experimentales de patología cardio-reno-vascular; Carditis y arteritis de origen hormanal alérgico tóxico, Portugal.
81. Bouchard, F., Limón Lason, R., and Rubio Alvarez, V.: Hipertensión arterial pulmonar aislada, Inst. Nac. de Card. México.
82. Dumarco, J., and Rimini, R.: La presión venosa en las extremidades, Uruguay.
83. Canabal, E. J., and Dighiero, J.: Bradicardia congénita familiar por disociación auriculoventricular completa, Uruguay.
84. Juncadella Ferrer, E.: Resultado del estudio de 15 accesos completos de taquicardia paroxística registrados en un caso de W. P. W., España.
85. Moia, B., Rosenbaum, M. B., and Baudino, C.: El voltaje del electrocardiograma precordial en el diagnóstico de hipertrofia ventricular izquierda, Argentina.
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Notice

The International Society of Angiology will hold a meeting on June 9, 1951, at the Claridge Hotel, Atlantic City, N. J. The meeting will be devoted to a scientific program and a business session. Further information may be obtained from Dr. Henry Haimovici, Secretary, 105 East 90th St., New York 28, N. Y.

Book Review

BASIC PRINCIPLES OF CLINICAL ELECTROCARDIOGRAPHY. By Hans H. Hecht. Springfield, Ill., Charles C Thomas, Publisher, 88 pages with 32 figures.

This is a monograph of the series "American Lectures in Circulation," simultaneously published by Blackwell Scientific Publications (Oxford) and the Ryerson Press (Toronto). The figures are almost always comprehensible at first sight. There is a brief and select bibliography. There is a short glossary at the end of the book which is useful for comprehension of the text. It is the purpose of this monograph to give a scientific basis for the clinical study of the electrocardiogram, showing the relationship between direct, semidirect, and bipolar leads, and the vectorcardiogram. The author tends to simplify the facts.

Sometimes these simplifications are useful for practical purposes even if not fully correct. So, when the author says that "the e.m.f. transmitted from the heart to the periphery may be likened to the waves of a radio sender or to the spreading waves of a lake . . .," he overlooks the fact that these forces are bipoles, not unipoles. The absence of resistors in the central terminal when electrocardiographs with high internal resistance are employed is useful and practical advice, even if not absolutely void of error (especially when Goldberger's connections are employed).

In other parts, the simplifications fall in error from the viewpoint of physics and mathematics, thus giving to the reader a false sense of security and the basis for future dogmatism. For instance, when he says: "Incidentally, the accuracy with which such reconstructions may be made (those of the standard limb leads from unipolar limb leads) furnishes another proof that the central terminal electrode . . . must be void of significant variations in electrical potentials throughout the cardiac cycle," he forgets that such reconstructions are merely a corollary of Kirchhoff's law and they continue to be true for a nonequilateral triangle, a nonhomogeneous medium, and an eccentrically placed heart, which would invalidate the zero value of the central terminal. The same misconception appears when, explaining "Einthoven's Law," he considers the differences in temperature between New York, Washington, and Los Angeles and states that ". . . the law which permits the calculation . . . holds true only if the source of energy (the sun or the heart) is equidistant from the points . . .." The following statement is likewise inacceptable: "It is obvious that the area enclosed by a vectorcardiogram is identical with the mean electrical axis for any given deflection." Here, two different kinds of bidimensional units are confused. In a vectorcardiogram both dimensions are differences of potential referred to space, while in a mean axis obtained from the "area" enclosed by a given deflection there is a combination of voltage and time measurements.

Finally, the monograph tends to schematize the facts and tries to find specific differences where there are but differences of appreciation. This leads the author to say that "a vectorcardiogram is to be viewed as an integration of two standard leads in much the same way that the standard leads represent the summation of two unipolar limb leads." With an equal amount of truthfulness or error one could say that the vectorcardiogram is an integration of two unipolar limb leads or of one of these and one bipolar lead and that unipolar limb leads represent the summation of two standard leads. To describe Lead II as the potential variations of the diaphragmatic surface minus those of the endocardial surface is a disorienting description, although correct, just as it would be to consider V_L as the potential variations of the left lateral surface minus those of the right one-half of the diaphragmatic surface. Unipolar and bipolar limb leads explore the heart in a similar way, but from different angles. Just as it is necessary to obtain V_L and V_F in order to evaluate Lead III or to obtain V_L and V_R to evaluate Lead I, it is convenient to obtain Leads I and III to evaluate V_L or to obtain Leads II and III to evaluate V_F. We feel that with these peculiarities the monograph will give a schematic and inadequate idea of Wilson's electrocardiographic discoveries.

E. C.